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1 519 495

PATENT SPECIFICATION

(11) 1 519 495

(19)

(21) Application No. 28394/75 (22) Filed 4 July 1975
(31) Convention Application No. 49/077 091
(32) Filed 4 July 1974
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(32) Filed 24 July 1974
(31) Convention Application No. 49/088 452
(32) Filed 31 July 1974
(31) Convention Application No. 50/002 650
(32) Filed 23 Dec. 1974
(31) Convention Application No. 49/077 091
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(31) Convention Application No. 49/077 091
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(31) Convention Application No. 49/077 091
(32) Filed 21 Jan. 1975
(31) Convention Application No. 49/088 452
(32) Filed 6 Feb. 1975
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(32) Filed 20 Feb. 1975
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(32) Filed 23 May 1975 in
(33) Japan (JP)
(44) Complete Specification published 26 July 1978
(51) INT CL^2 C07D 205/08, 401/12, 403/02, 405/12, 409/00, 411/12, 413/12, 417/12, 473/00//A61K 31/395 (C07D 401/12, 213/02) (C07D 403/02, 209/04, 209/48, 239/02, 249/18, 257/04) (C07D 405/12, 307/34, 309/16) (C07D 409/00, 205/08, 333/04) (C07D 411/12, 327/06) (C07D 413/12, 261/02, 263/00, 271/02, 295/00) (C07D 417/12, 285/04) (C07D 473/00, 233/88, 239/48)
(52) Index at acceptance
C2C 1200 1310 1343 1344 1370 1371 1372 1422 1430 1432 1440 1452 1464 1470 1510 1530 1562 1601 1671 1680 200 213 214 215 220 222 225 226 22Y 246 247 250 251 252 253 254 255 256 25X 25Y 270 271 280 281 282 28X 290 292 29X 29Y 305 30Y 311 313 314 31Y 320 321 322 323 324 326 327 32Y 332 334 338 339 340 341 342 345 346 34Y 350 351 352 354 355 358 360 361 362 364 365 366 367 368 36Y 373 37Y 380 385 389 394 395 397 39Y 43X 440 490 509 50Y 510 511 512 519 51X 531 535 575 576 57Y 588 58Y 596 601 603 604 60X 60Y 612 613 614 620 623 624 625 626 627 628 62X 635 636 638 63X 645 648 64X 650 652 658 65X 662 668 670 678 682 68X 695 699 70Y 71X 71Y 72X 72Y 73X 750 751 754 75X 761 762 763 76X 76Y 78X 78Y 790 79Y KA KB KD KM KN KR KS KW KZ LZ RC RD RE RF SD SG SJ SL SM TP

(54) AZETIDINONE DERIVATIVES AND PROCESS FOR PREPARATION THEREOF

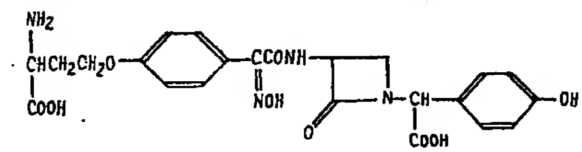
(71) We, FUJISAWA PHARMACEUTICAL CO. LTD., a Japanese Company of 3, Doshomachi, 4-chome, Higashiku, Osaka, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

BACKGROUND OF THE INVENTION:

The present invention is based on the success of identification of the chemical structure of FR—1923 substance. That is, FR—1923 substance is a known antibiotic isolated from the fermentation broth of a strain of the genus *Nocardia* deposited with the American Type Culture Collection under ATCC No. 21806, the details of which are described for example, in German Patent Specification No. 2,242,699.

In said prior literature, the FR—1923 substance is defined by the various physicochemical properties without any disclosure of its chemical structure.

As a result of extensive investigations, the inventors of the present invention have succeeded in identifying the chemical structure of the FR—1923 substance and assigning the following chemical structure and name to said substance.

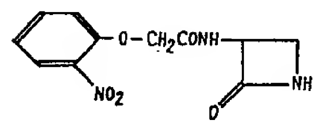


FR—1923 substance

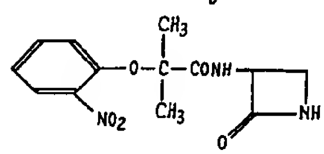
1 - (α - Carboxy - 4 - hydroxybenzyl) - 3 - [2 - {4 - (3 - amino - 3 - carboxypropoxy)-phenyl} - 2 - hydroxyiminoacetamido] - 2 - azetidinone

The above new discovery and knowledge gave the inventors of the present invention the possibility of studying some chemical modifications of FR—1923 substance for the first time. Then, based on such facts, the inventors have been making a study of said modification so that they have just succeeded in synthesizing a lot of novel and unique modified compounds derived from FR—1923 substance and the related compounds.

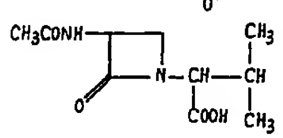
Only for the purpose of illustrating the state of the arts, the known compounds derived from penicillins and the relevant literatures are mentioned as follows.



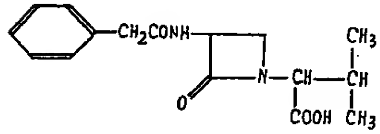
(U.S.P. 3487,072)



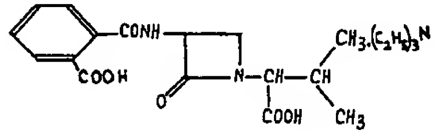
(Journal of Organic Chemistry, Vol. 38, p. 940—943, 1973)



(Archir Der Pharmazie und Berichte der Deutschen Pharmazeutischen Gesellschaft, Vol. 303, p 831—835)



(Chemistry of Penicillin (Princeton University Press) p 973—1003)



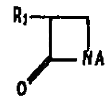
(Archir Der Pharmazie und Berichte der Deutschen Pharmazentischen Gesellschaft, Vol. 303(p 831—835)

The present invention relates to azetidinone derivatives. More particularly, it relates to novel azetidinone derivatives having antimicrobial activities and to process for preparation thereof.

Accordingly, it is an object of the present invention to provide azetidinone derivatives having antimicrobial activities.

Another object of the present invention is to provide a process for preparation of the azetidinone derivatives.

The present invention provides a compound of the formula:



(I)

or its salt
wherein

R_1 is amino or acylamino,

A is hydrogen,

a saturated or unsaturated normal aliphatic hydrocarbon residue, which is substituted by at least one substituent of carboxy or its derivatives, cyano, hydroxy and amino,

an unsaturated branched aliphatic hydrocarbon residue which is substituted by at least one substituent of carboxy, or its derivatives, cyano, hydroxy and amino, or

an aliphatic hydrocarbon residue which is substituted by carboxy or its derivatives at the first position thereof and by phenyl at the first position thereof whose ring may be substituted by one or more substituents selected from hydroxy, amino, nitro, alkyl, alkoxy, aralkoxy, alkylthio, halogen and sulfo; provided that when R_1 is 2-[4-(3-amino-3-carboxypropoxy)phenyl]-2-hydroxyiminoacetamido,

A is hydrogen,

a saturated or unsaturated normal aliphatic hydrocarbon residue, which is substituted by at least one substituent of carboxy or its derivatives, cyano, hydroxy and amino,

an unsaturated branched aliphatic hydrocarbon residue which is substituted by at least one substituent of carboxy or its derivatives, cyano, hydroxy and amino, or

an aliphatic-hydrocarbon residue which is substituted by carboxy or its derivatives at the first position thereof and by phenyl at the first position thereof whose ring may be substituted by one or more substituents selected from amino, nitro, alkyl, alkoxy, aralkoxy, alkylthio, halogen and sulfo,

when

R_1 is 2-(2-nitrophenoxy)acetamido or 2-(2-nitrophenoxy)-2-methylpropionamido,

A is

a saturated or unsaturated normal aliphatic-hydrocarbon residue which is substituted by at least one substituent of carboxy or its derivatives, cyano, hydroxy and amino,

an unsaturated branched aliphatic hydrocarbon residue, which is substituted by at least one substituent of carboxy or its derivatives, cyano, hydroxy and amino, or

an aliphatic hydrocarbon residue which is substituted by carboxy or its derivatives at the first carbon thereof and by phenyl at the first carbon thereof, whose ring may be substituted by one or more substituents selected from hydroxy, amino, nitro, alkyl, alkoxy, aralkoxy, alkylthio, halogen and sulfo, and

when

R^1 is phenylacetamido,

A is hydrogen,

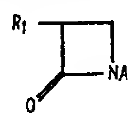
a saturated or unsaturated normal aliphatic hydrocarbon residue, which is substituted by at least one substituent of carboxy or its derivatives, cyano, hydroxy and amino, or

an aliphatic hydrocarbon residue which is substituted by carboxy or its derivatives at the first position thereof and by phenyl at the first position thereof, whose ring may be substituted by one or more substituents selected from hydroxy, amino, nitro, alkyl, alkoxy, aralkoxy, alkylthio, halogen and sulfo,

when

A is hydrogen, R_1 is not formamido, benzyloxycarbonylamino or phthalimido.

In another aspect the invention provides a compound of the formula:

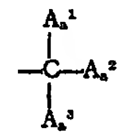


wherein

R_1 is amino or acylamino, and

A is hydrogen or

a group of the formula:



in which

A_a^1 is hydrogen and

A_a^2 is hydrogen or phenyl which may be substituted by at least one substituent selected from hydroxy, amino, nitro, alkyl, alkoxy, aralkoxy, alkylthio and halogen or

A_a^1 and A_a^2 together form alkylidene, and

A_a^3 is carboxy or its derivatives, or cyano,

provided that,

when

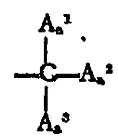
R_1 is 2-[4-(3-amino-3-carboxypropoxy)phenyl]-2-hydroxyiminoacetamido,

A is not α-carboxy-4-hydroxybenzyl or its derivatives at the carboxy group;

when

R_1 is 2-(2-nitrophenoxy)acetamido, 2-(2-nitrophenoxy)-2-2-methylpropionamido, formamido, benzyloxycarbonylamino or phthalimido,

A is a group of the formula:



in which

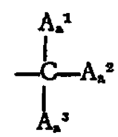
A_a^1, A_a^2 and A_a^3 are as defined above, and

when

R_1 is phenylacetamido,

A is hydrogen, or

a group of the formula:



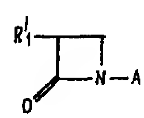
in which

A_a^1 is hydrogn,

A_a^2 is hydrogen or phenyl which may be substituted by at least one substituent selected from hydroxy, amino, nitro, alkyl, alkoxy, aralkoxy, alkylthio, and halogen, and

A_a^3 is as defined above.

In another aspect the invention provides a process for preparing a compound of the formula:



wherein

R_1' is acylamino, and

A is hydrogen,

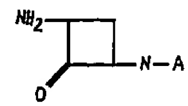
a saturated or unsaturated normal aliphatic hydrocarbon residue, which is substituted by at least one substituent fo carboxy or its derivatives, cyano, hydroxy and amino,

a saturated branched aliphatic hydrocarbon residue which is substituted by at least one substituent of carboxy or its derivatives, cyano, hydroxy and amino,

an unsaturated branched aliphatic hydrocarbon residue which is substituted by at least one substituent of carboxy or its derivatives, cyano, hydroxy and amino, or

an aliphatic hydrocarbon residue substituted by carboxy or its derivatives at the first position thereof and by phenyl at the first position thereof, which may be substituted by one or more substituents selected from hydroxy, amino, nitro, alkyl, alkoxy, aralkoxy, alkylthio, halogen and sulfo;

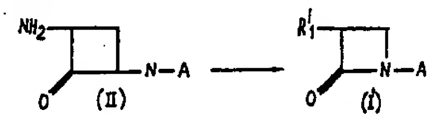
which comprises reacting a compound of the formula:



wherein A is as defined above, with an acylating agent.

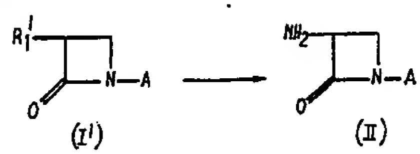
According to the present invention, the azetidinone derivatives (I) can be prepared by various methods, which are illustrated collectively by the following scheme for convenience's sake.

(1) Process 1:

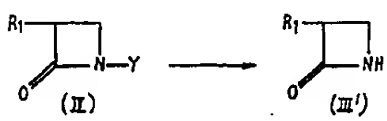


(2) Process 2:

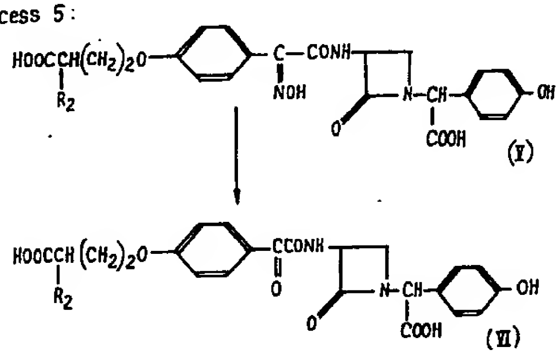
(3) Process 3:



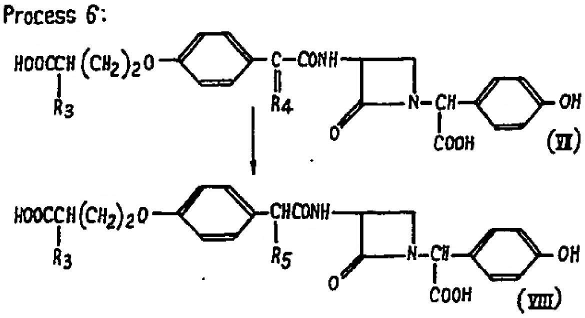
(4) Process 4:



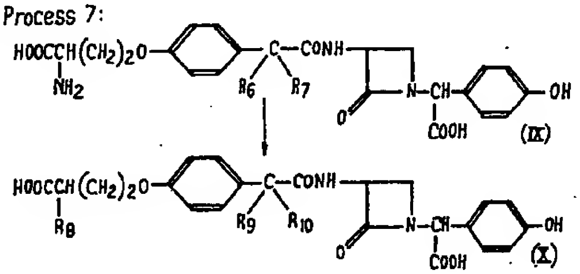
(5) Process 5:



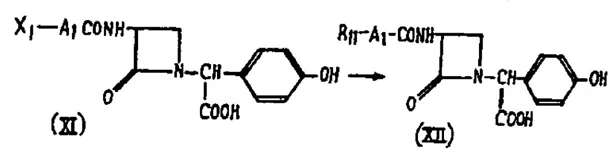
(6) Process 6:



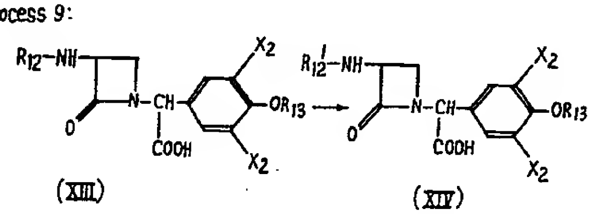
(7) Process 7:



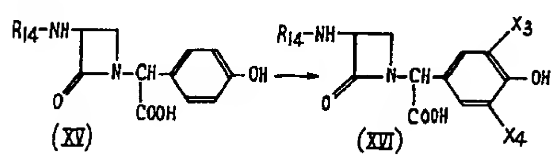
(8) Process 8:



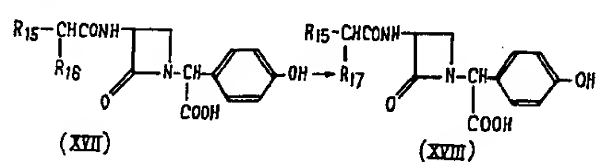
(9) Process 9:



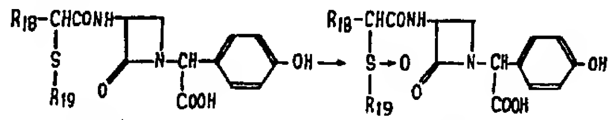
(10) Process 10:



(11) Process 11:

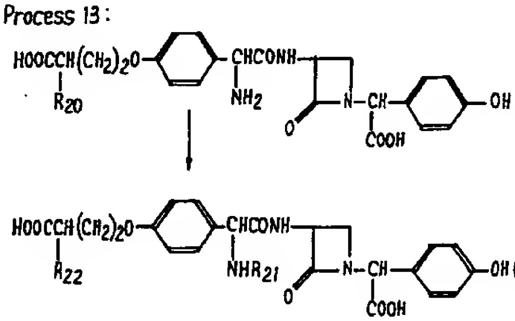


(12) Process 12:



(XIX) (XX)

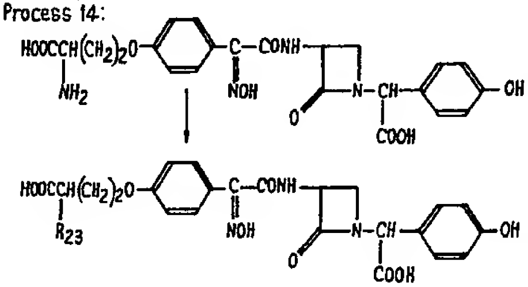
(13) Process 13:



(XXI)

(XXII)

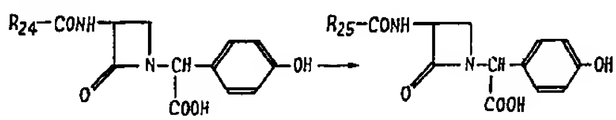
(14) Process 14:



(XXIII)

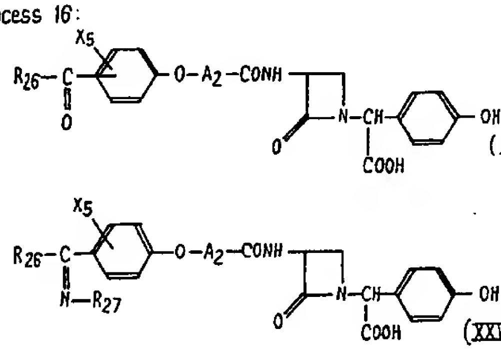
(XXIV)

(15) Process 15:



(XXV) (XXVI)

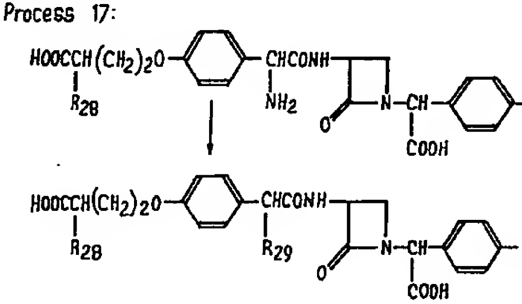
(16) Process 16:



(XXVII)

(XXVIII)

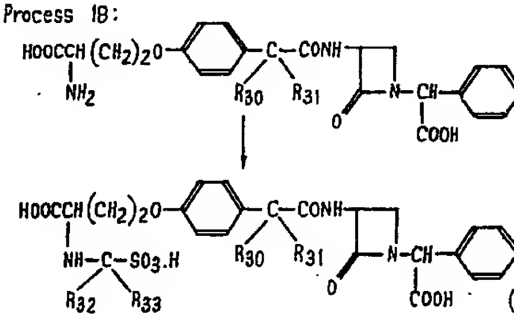
(17) Process 17:



(XXIX)

(XXX)

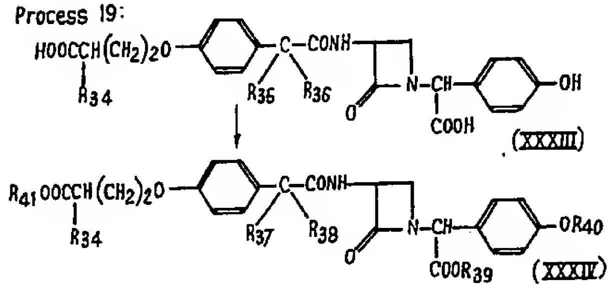
(18) Process 18:



(XXXI)

(XXXII)

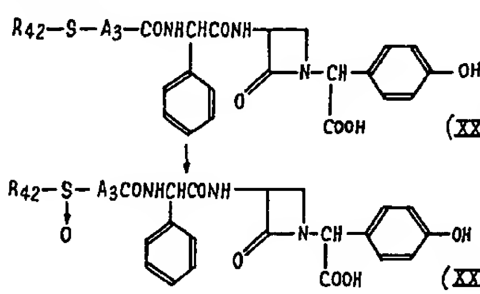
(19) Process 19:



(XXXIII)

(XXXIV)

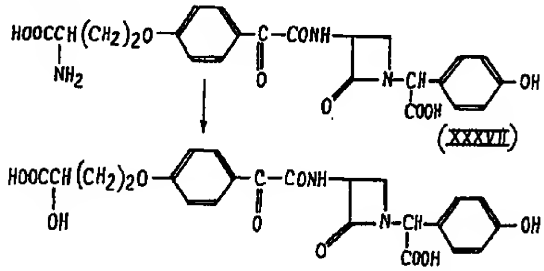
(20) Process 20:



(XXXV)

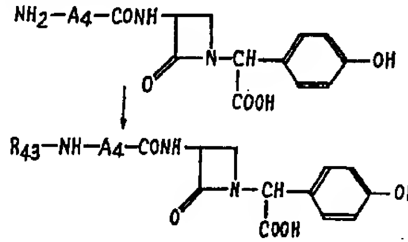
(XXXVI)

(21) Process 21:



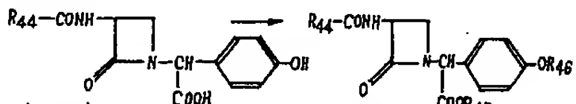
(XXXVII) (XXXVIII)

(22) Process 22:



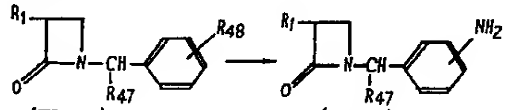
(XXXIX) (XXXX)

(23) Process 23:



(XXXXI) (XXXXII)

(24) Process 24:

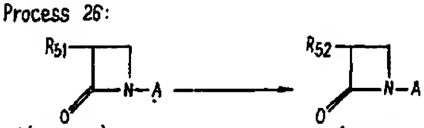


(XXXXIII) (XXXXIV)

(25) Process 25:

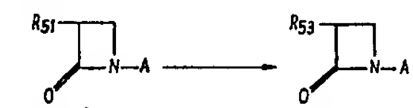
(XXXXV) (XXXXVI)

(26) Process 26:



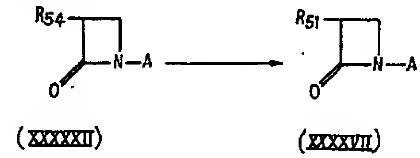
(XXXXVII) (XXXXVIII)

(27) Process 27:

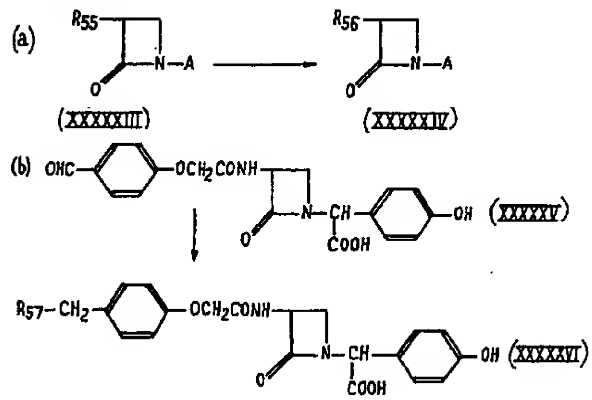


(XXXXVII) (XXXXIX)

(28) Process 28:



(29) Process 29:



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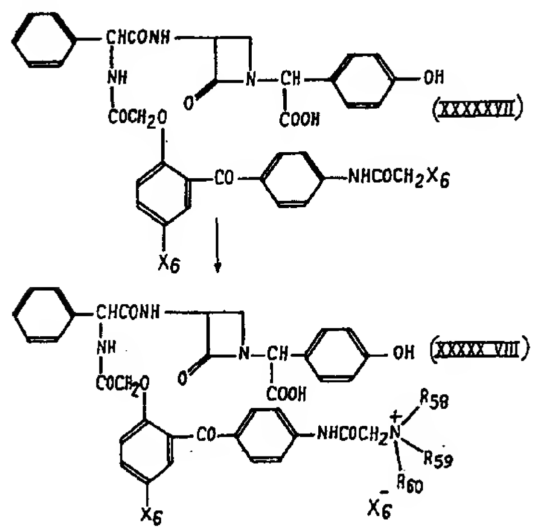

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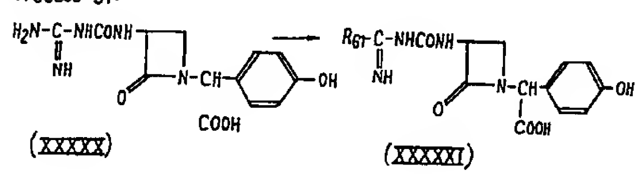


With regard to the process as illustrated above, it is to be understood that the Process 1 and Process 2 are fundamental process and the remaining Processes are alternative ones.

The definitions of the symbols used in the above formulae are mentioned in the following.

R_1 is as defined above;
A is as defined above;
A′ is as defined in the symbol " A " excepting hydrogen;
R_1' is acylamino;
Y is oxalo, esterified oxalo, or alkyl whose first carbon is substituted by protected amino or protected hydroxy;
R_2 is amino or acylamino;
R_3 is amino or acylamino;
R_4 is oxo or hydroxyimino;
R_5 is amino or hydroxy;
R_6 and R_7 are combined to form oxo or hydroxyimino, or R_6 is hydrogen, and R_7 is amino or hydroxy;
R_8 is acylamino;
R_9 and R_{10} are combined to form oxo or hydroxyimino, or R_9 is hydrogen and R_{10} is amino, hydroxy, acylamino or acyloxy;
X_1 is acid residue;
A_1 is bivalent aliphatic hydrocarbon radical;
R_{11} is residue of nucleophile;
R_{12} is acyl having protected amino, protected hydroxy or protected carboxy function(s);
R_{12}' is acyl having amino, hydroxy or carboxy function(s);
R_{13} is hydrogen or alkyl;
X_2 is hydrogen or halogen;
R_{14} is acyl;
X_3 is hydrogen or halogen;
X_4 is halogen;
R_{15} is hydrogen, alkyl, aryl, aralkyl, aryloxy, heterocyclic group or heterocyclic alkyl;
R_{16} is amino or hydrocarbon residue having amino;
R_{17} is acylamino or acylamino-substituted-hydrocarbon residue;
R_{18} is hydrogen or aryl;
R_{19} is alkyl, N-arylcarbamoylalkyl or aryl;
R_{20} is amino or acylamino;
R_{21} is aryl substituted by at least one substituent of nitro and esterified carboxy;
R_{22} is arylamino whose aryl ring is substituted by at least one substituent of nitro and esterified carboxy, or acylamino;
R_{23} is mono- or di-alkylamino;
R_{24} is nitroaryl;
R_{25} is aminoaryl;
R_{26} is hydrogen or aryl;
X_5 is hydrogen or halogen;
A_2 is bivalent aliphatic hydrocarbon radical;
R_{27} is hydroxy, alkoxy or alkanoylamino;
R_{28} is acylamino;
R_{29} is acylamino;
R_{30} and R_{31} are combined to form oxo or hydroxyimino, or R_{30} is hydrogen and R_{31} is hydroxy;
R_{32} and R_{33} are hydrogen or alkyl;
R_{34} is acylamino;
R_{35} and R_{36} are combined to form oxo or hydroxyimino, or R_{35} is hydrogen and R_{36} is acylamino or hydroxy;
R_{37} and R_{38} are combined to form oxo, hydroxyimino, alkoxyimino, or substituted alkoxyimino or, R_{37} is hydrogen and R_{38} is acylamino, hydroxy, alkoxy or acyloxyalkoxy;
R_{39} is alkyl or substituted alkyl;
R_{40} is hydrogen, alkyl or aralkyl;
R_{41} is alkyl or substituted alkyl;
R_{42} is alkyl, aryl or aralkyl;
A_3 is alkylene;
A_4 is bivalent aliphatic hydrocarbon radical;

R_{43} is aryl, substituted by at least one substituent of nitro and esterified carboxy or aromatic heterocyclic group;

R_{44} is aralkyl;

R_{45} is alkyl;

R_{46} is hydrogen or alkyl;

R_{47} is carboxy or its derivative;

R_{48} is a protected amino;

R_{49} is an acylamino having carboxy or its reactive derivative;

R_{50} is an acylamino having carbazoyl, N-(hydroxyalkyl)carbamoyl or N-aralkylcarbamoyl;

R_{51} is an acylamino having amino;

R_{52} is an acylamino having esterified carboxyalkylamino;

R_{53} is an acylamino having alkenyl substituted by esterified carboxy;

R_{54} is an acylamino having nitro or azido;

R_{55} is an acylamino having one group selected from formyl, alkanoyl and aroyl;

R_{56} is an acylamino having hydroxyalkyl or α-hydroxyaralkyl;

R_{57} is aralkylamino;

X_6 is halogen;

R_{58}, R_{59} and R_{60} are each alkyl; and

R_{61} is aralkanoylamino;

Examples of the definitions for the above symbols are illustrated below, respectively. With respect to the compounds (I), (III'), (IV), (XXXXIII) and (XXXXIV).

An acyl moiety in the acylamino for R_1 may include an aliphatic acyl, an aromatic acyl, a heterocyclic acyl and an aliphatic acyl whose aliphatic moiety is substituted by aromatic group or heterocyclic group. Examples of such acyl are illustrated in the following;

An aliphatic moiety in said *aliphatic* acyl may include saturated or unsaturated acyclic or cyclic hydrocarbon residue, in which the acyclic hydrocarbon residue may be branched and partially cyclized. Suitable examples of said acyclic or alicyclic hydrocarbon residue (hereinafter referred to aliphatic-hydrocarbon residue) are mentioned in more concrete as follows.

— alkyl (e.g., methyl, ethyl, propyl, butyl, isobutyl, pentyl, neopentyl, octyl, undecyl, tridecyl, pentadecyl, cyclohexylmethyl, cyclohexylethyl, bornanyl);
— alkenyl (e.g., vinyl, propenyl, isopropenyl, 3-methylbutenyl, butenyl, 2-methylpropenyl, pentenyl, octadecenyl, 3-cyclohexenylmethyl);
— alkynyl (e.g., ethynyl, 2-propynyl);
— cycloalkyl (e.g., cyclopropyl, cyclopentyl, cyclohexyl, indanyl, bornyl, adamantyl); and
— cycloalkenyl (e.g., 1-cyclopenten-1-yl, 2-cyclopenten-1-yl, 3-cyclohexene-1-yl, bornenyl).

A suitable aromatic group in said *aromatic* acyl may include aryl such as phenyl, tolyl (or) naphthyl.

A heterocyclic group in said *heterocyclic* acyl may include monocyclic or polycyclic heterocyclic group containing at least one hetero-atom such as oxygen, sulfur or nitrogen. Suitable examples of said heterocyclic group are mentioned in more concrete as follows.

— a 3- to 8- membered monocyclic heterocyclic group containing at least one sulfur atom (e.g., thienyl dihydrothiopyranyl);
— a 3- to 8- membered monocyclic heterocyclic group containing at least one oxygen atom (e.g., oxiranyl, furyl, dihydrofuryl, pyranyl, dihydropyranyl, tetrahydropyranyl, dioxanyl);
— a 3- to 8- membered monocyclic heterocyclic group containing at least one nitrogen atom (e.g., aziridinyl, azetidinyl, pyrrolyl, 2- or 3H-pyrrolyl, 2 or 3 pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolidinyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, piperidinyl, pyridazinyl, tetrazolyl);
— a 3- to 8- membered monocyclic heterocyclic group containing at least one oxygen atom and at least one nitrogen atom (e.g., oxazolyl, isoxazolyl, oxadiazolyl, sydnonyl);
— a 3- to 8- membered monocyclic heterocyclic group containing at least one sulfur atom and at least one nitrogen atom (e.g., thiazolyl, isothiazolyl, thiadiazolyl);
— a polycyclic heterocyclic group containing at least one sulfur atom (e.g., benzene-fused heterocyclic group such as benzothienyl, benzothiopyranyl);
— a polycycle heterocyclic group containing at least one nitrogen atom (e.g., indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinoyl, dihydroisoquinolyl, quinazolyl, 1 or 2H-indazolyl, 1 or 2H-benzotriazolyl, purinyl, carbazolyl);

— a polycyclic heterocyclic group containing at least one oxygen atom and at least one nitrogen atom (e.g.) benzoxazolyl, benzoxadiazolyl); and

— a polycyclic heterocyclic group containing at least one sulfur atom and at least one nitrogen atom (e.g., benzothiazolyl, benzothiadiazolyl).

An aliphatic moiety in said *aliphatic* acyl whose aliphatic moiety is substituted by aromatic group or heterocyclic group is intended to mean the same meaning as defined in the above explanation of the aliphatic moiety in the aliphatic acyl, and include the same suitable examples thereof as stated in more concrete above. And in the same manner, each of the aromatic group and an heterocyclic group also is intended to mean the same meaning as defined in the above explanation of the aromatic group in the aromatic acyl and of the heterocyclic group in the heterocyclic acyl as well, and include the same suitable examples thereof as stated in mode concrete above, respectively.

The optional carbon atom of the aliphatic acyl as defined above may be replaced and/or interrupted by one or more radicals selected from a bivalent aromatic radical, a bivalent heterocyclic radical, —O—, —N=, —S—, —SO—, $—SO_2—$, and —NH— whose hydrogen atom may be replaced by alkyl or aryl.

Each of the aliphatic moiety, aromatic group and heterocyclic group in the aliphatic acylamino, the aromatic acylamino, the heterocyclic acylamino and the aliphatic acylamino whose aliphatic moiety is substituted by aromatic group or heterocyclic group as defined above may optionally be substituted by one or more substituents selected from halogen, nitro, amino, carboxy, esterifiedcarboxy, hydroxy, $—N_3$, —CN, $—NHNH_2$, =O, =NH, =S, sulfo and =NOH whose hydrogen atom may be replaced by alkyl or aralkyl, and the said heterocyclic group in the foregoing acylamino group may optionally be substituted by alkyl and/or an aromatic group.

Particularly suitable examples of the aforementioned acylamino for R_1 may be illustrated as follows.

— alkanoylamino;

— alkenoylamino;

— aroylamino;

— heterocycle carbonylamino;

— alkanoylamino substituted by aryl or heterocyclic group;

— alkenoylamino substituted by aryl or heterocyclic group;

— alkanoyl or alkenyl amino, whose optional carbon chain(s) is interrupted by bivalent-aromatic radical and/or bivalentheterocyclic radical;

— alkanoyl or alkenyl amino substituted by aryl and/or heterocyclic group, in which an optional carbon chain(s) of the acyclic hydrocarbon moiety is interrupted by bivalent-aromatic radical and/or bivalent-heterocyclic radical;

— alkanoyl or alkenyl amino substituted by aryl and/or heterocyclic group, in which an optional carbon chain(s) of the acyclic hydrocarbon moiety is interrupted by one or more radicals selected from —O—, —N=, —S—,

$$\underset{\downarrow}{—S—},\atop O$$

$—SO_2—$, and —NH— whose hydrogen atom may be replaced by alkyl or aryl;

— alkanoyl or alkenoyl amino substituted by aryl and/or heterocyclic group, in which an optional carbon chain(s) of the acyclic hydrocarbon moiety is interrupted by aromatic radical and/or bivalent heterocyclic radical, and further is interrupted by one or more radicals selected from —O—, —N=, —S—,

$$\underset{\downarrow}{—S—},\atop O$$

$—SO_2—$, and —NH— whose hydrogen atom may be replaced by alkyl or aryl;

— alkanoyl or alkenyl amino whose optional carbon chain is interrupted by one or more radicals selected from —O—, —N=, —S—,

$$\underset{\downarrow}{—S—},\atop O$$

$—SO_2—$, and —NH— whose hydrogen atom may be replaced by alkyl or aryl;

— alkanoyl or alkenoyl amino whose optional carbon chain is interrupted by bivalent-

aromatic radical and/or bivalent heterocyclic radical and further interrupted by one or more radicals selected from —O—, —N=, —S—,

$$\underset{\substack{\downarrow\\ \mathrm{O}}}{\text{—S—}},$$

—SO_2—, and —NH— whose hydrogen atom may be replaced by alkyl or aryl;

— aroylamino or heterocycle carbonylamino, in which the bond between the ring and the carbonyl is interrupted by one or more radicals selected from —O—, —N=, —S—,

$$\underset{\substack{\downarrow\\ \mathrm{O}}}{\text{—S—}},$$

—SO_2—, and —NH—, whose hydrogen atom may be replaced by alkyl or aryl;

— alkanoyl or alkenoyl amino substituted by cycloalkyl, aryl and/or heterocyclic group, in which the bond between such ring and the acyclic hydrocarbon moiety is interrupted by one or more radicals selected from —O—, —N=, —S—,

$$\underset{\substack{\downarrow\\ \mathrm{O}}}{\text{—S—}},$$

SO_2, and —NH—, whose hydrogen atom may be replaced by alkyl or aryl;

— alkanoyl or alkenoyl amino substituted by cycloalkyl, aryl and/or heterocyclic group, in which each of the bond between the ring and the acyclic hydrocarbon moiety and an optional carbon chain of the acyclic hydrocarbon moiety is interrupted by bivalent-aromatic radical and/or bivalent heterocyclic radical, and/or one or more radicals selected from —O—, —N=, —S—,

$$\underset{\substack{\downarrow\\ \mathrm{O}}}{\text{—S—}},$$

—SO_2— and —NH—, whose hydrogen atom may be replaced by alkyl or aryl,

— aroylamino or heterocycle carbonylamino in which the bond between the ring and the carbonyl is interrupted by one or more bivalent-aromatic radical and/or bivalent-heterocyclic radical;

— alkanoyl or alkenoyl amino substituted by aryl and/or heterocyclic group, in which the bond between the ring and the acyclic hydrocarbon moiety are interrupted by bivalent-aromatic radical and/or bivalent-heterocyclic radical, and further one or more radicals selected from —O—, —N=, —S—,

$$\underset{\substack{\downarrow\\ \mathrm{O}}}{\text{—S—}},$$

—SO_2— and —NH—, whose hydrogen atom may be replaced by alkyl or aryl, and

— alkanoyl or alkenoyl amino substituted by aryl and/or heterocyclic group, in which the bond between the ring and the acyclic hydrocarbon moiety is interrupted by one or more bivalent-aromatic radicals and/or bivalent-heterocyclic radicals;

An optional carbon atom of above defined acylamino group may be substituted by one or more substituents selected from halogen, nitro, amino, carboxy, esterified carboxy, hydroxy, —N_3, —CN, —$NHNH_2$, =O, =NH, =S, sulfo, =NOH whose hydrogen atom may be replaced by alkyl or aralkyl, and the heterocyclic group in the foregoing acylamino group may optionally be substituted by alkyl.

More particularly suitable examples of the acylamino for R_1 may be illustrated as follows:

— alkanoylamino, in which an optional carbon chain is interrupted by one phenylene and further optional carbon atoms are substituted by one halogen and one oxo;

— phenylalkanoylamino, in which an optional carbon atom may be substituted by one substituent selected from amino, carboxy, esterified carboxy, hydroxy, halogen, nitro, sulfo, oxo, hydroxyimino and benzyloxyimino;

— naphthylalkanoylamino;

- dihydropyranylalkanoylamino, in which an optional carbon atom is substituted by one hydroxy;
- morpholinoalkanoylamino;
- thienylalkanoylamino in which an optional carbon atom may be substituted by one substituent selected from amino, hydroxy, oxo and hydroxyimino;
- furylalkanoylamino;
- tetrazolylalkanoylamino;
- indolylalkanoylamino, in which an optional carbon atom is substituted by one amino;
- diphenylalkanoylamino;
- alkanoylamino substituted by phenyl and thienyl;
- 3-alkyl-1,2,5-oxadiazol-4-yl-alkanoylamino;
- phenylalkenoylamino;
- phenylalkanoylamino, in which an optional carbon chain of the alkane moiety is interrupted by one phenylene;
- phenylalkanoylamino, in which an optional carbon chain of the alkane moiety is interrupted by one or two bivalent radicals selected from —O—, —N=, —S—, —NH—,

$$\underset{\displaystyle CH_3}{\overset{}{-\underset{|}{N}-}} \quad \text{and} \quad \underset{\displaystyle O}{-\underset{\downarrow}{S}-},$$

  and further an optional carbon atom(s) of the group thus defined may be substituted by one to four substituents selected from amino, carboxy, esterified carboxy, halogen, oxo and =NH;
- thienylalkanoylamino, in which an optional carbon chain(s) of the alkane moiety is interrupted by one to two bivalent radicals selected from —O—, —S— and —NH—, and further an optional carbon atom(s) of the group thus defined is substituted by one to four substituents selected from amino, carboxy, halogen and oxo;
- dihydropyranylalkanoylamino, in which an optional carbon chain of the alkane moiety is interrupted by —NH— and an optional carbon atom of the group thus defined is substituted by halogen;
- diphenylalkanoylamino, in which an optional carbon chain(s) of the alkane moiety is interrupted by one to three bivalent radicals selected from —O—, —N= and —NH—, and further an optional carbon atom(s) of the group thus defined may be substituted by one or two substituents selected from carboxy, hydroxy and oxo;
- alkanoylamino substituted by phenyl and thienyl, in which an optional carbon chain(s) of the alkane moiety is interrupted by one to two bivalent radicals selected from —O—, —N= and —NH—, and further an optional carbon atom(s) of the group thus defined may be substituted by one to five substituents selected from amino, halogen, oxo and thioxo;
- alkanoylamino substituted by phenyl and indolyl, in which an optional carbon chain(s) of the alkane moiety is interrupted by one —O— and one —NH—, and further an optional carbon atom of the group thus defined is substituted by one oxo;
- alkanoylamino substituted by phenyl and benzo[d]isoxazolyl, in which an optional carbon chain(s) of the alkane moiety is interrupted by one —O— and one —NH—, and further an optional carbon atom of the group thus defined is substituted by one oxo;
- phenylalkanoylamino, in which an optional carbon chain(s) of the alkane moiety is interrupted by one or two bivalent radicals selected from phenylene, 2-oxo-azetidin-1,3-diyl, 1,3,4-thiadiazol-1,5-diyl and 1,3-oxazolidin-3,4-diyl and one to four bivalent radicals selected from —O—, —N=, —S—, —NH— and

$$\underset{\displaystyle CH_3}{-\underset{|}{N}-},$$

  and further an optional atom(s) of the group thus defined may be substituted by one to six substituents selected from amino, halogen, hydroxy, esterified carboxy, oxo, hydroxyimino, benzyloxyimino and hydrazino;
- thienylalkanoylamino, in which an optional carbon chain(s) of the alkane moiety is interrupted by one phenylene, and two bivalent radicals selected from —O—

and —NH— and further an optional carbon atom(s) of the group thus defined is substituted by carboxy, oxo and hydroxyimino;

— benzo[c]pyrrolidinylalkanoylamino, in which an optional carbon chain of the alkane moiety is interrupted by one phenylene and one —O—, and further optional carbon atoms of the group thus defined are substituted by four substituents selected from amino, carboxy, hydroxy, esterified carboxy, oxo, hydroxyimino and methoxyimino;

— diphenylalkanoylamino, in which optional carbon chains of the alkane moiety are interrupted by one phenylene and one —O— and one —NH—, and further an optional carbon atom(s) of the group thus defined is substituted by two to four substituents selected from amino, halogen, nitro, oxo and hydroxyimino;

— alkanoylamino substituted by phenyl and furyl, in which optional carbon chains of the alkane moiety are interrupted by one phenylene and one —NH— and one —O—, and further an optional carbon atom(s) of the group thus defined is substituted by three substituents selected from halogen and oxo;

— alkanoylamino, in which an optional carbon chain(s) is interrupted by one or two bivalent radicals selected from —O—, —S—, —NH—, —SO_2— and

and further an optional carbon atom(s) of the group thus defined may be substituted by one to two substituents selected from amino, azido, carboxy, hydroxy, oxo, thioxo and =NH;

— alkenoylamino, whose optional carbon chain is interrupted by one —S—;

— alkanoylamino, in which an optional carbon chain(s) is interrupted by one or two phenylenes and one to five bivalent radicals selected from —O—, —N=, —S—, —NH— and

$$-\overset{\displaystyle CH_3}{\overset{|}{N}}-,$$

and further an optional carbon atom(s) of the group thus defined may be substituted by one to seven substituents selected from amino, carboxy, hydroxy, halogen, azido, sulfo, esterified carboxy, oxo, thioxo, hydroxyimino and methoxyimino;

— alkanoylamino, in which an optional carbon chain is interrupted by one 1,3,4-thiadiazol-2,5-diyl and one or two bivalent radicals selected from —S— and —NH—, and further an optional carbon atom(s) of the group thus defined is substituted by one or six substituents selected from amino, hydroxy and oxo;

— alkenoylamino, in which an optional carbon chain is interrupted by one phenylene and one or two bivalent radicals selected from —O— and —NH—, and further an optional carbon atom(s) of the group thus defined is substituted by one or three substituents selected from carboxy, esterified carboxy, nitro, oxo and hydroxyimino;

— 1,2-oxazolidinylcarbonylamino, in which the bond between the 1,2-oxazolidinyl and the carbonyl is interrupted by —NH—, and further an optional carbon atom of the group thus defined is substituted by one oxo;

— bicyclo[2,2,1]heptylalkanoylamino, in which the bond between the bicyclo[2,2,1]-heptyl and the alkane moiety is interrupted by one —O—, and further an optional carbon atom(s) of the bicyclo[2,2,1]heptane ring is substituted by three alkyl;

— phenylalkanoylamino, in which the bond between the phenyl and the alkane moiety is interrupted by one or two bivalent radicals selected from —O—, —S—, —NH— and —SO_2—, and further an optional carbon atom of the group thus defined may be substituted by one substituent selected from halogen and nitro;

— naphthylalkanoylamino, in which the bond between the naphthyl and the alkane moiety is interrupted by one bivalent radical selected from —O— and —NH—;

— pyridylalkanoylamino, in which the bond between the pyridyl and the alkane moiety is interrupted by one —O—;

— 1,3,4-thiadiazolylalkanoylamino, in which the bond between the 1,3,4-thiadiazolyl and the alkane moiety is interrupted by one —S—;

— 1H-1,2,3-benzotriazolylalkanoylamino, in which the bond between the 1H-1,2,3-benzotriazolyl and the alkane moiety is interrupted by one —O—;

— pyridyl-1-oxidealkanoylamino, in which the bond between the pyridyl-1-oxide and the alkane moiety is interrupted by one —S—;

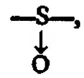
— diphenylalkanoylamino, in which the bond between the one or two phenyl and the alkane moiety is interrupted by one or two bivalent radicals selected from —O—, —S—, —NH— and —SO_2—, and further an optional carbon atom(s) of the group thus defined is substituted by one or two substituents selected from nitro, carboxy, halogen, hydroxy and oxo;

— alkanoylamino substituted by phenyl and naphthyl, in which the bond between the naphthyl and the alkane moiety is interrupted by one —O—;

— alkanoylamino substituted by phenyl and pyrimidinyl, in which the bond between the pyrimidinyl and the alkane moiety is interrupted by —S—, and further an optional carbon atom(s) of the group thus defined is substituted by one amino and one hydroxy;

— alkanoylamino substituted by bicyclo[2,2,-]heptyl and phenyl, in which the bond between the bicyclo[2,2,1]heptyl and the alkane moiety is interrupted by one —O— and an optional carbon chain of the alkane moiety is interrupted by one —NH—, and further an optional carbon atom of the alkane moiety is substituted by oxo and optional carbon atoms of the bicyclo[2,2,1]heptane ring are substituted by three alkyl,

— diphenylalkanoylamino, in which the bond between one of the diphenyl and the alkane moiety is interrupted by one or two bivalent radicals selected from —O—, —NH—, —S—,



—SO_2— and

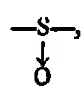
and an optional carbon chain of the alkane moiety is interrupted by one or two bivalent radicals selected from —NH— and —S—, and further an optional carbon atom(s) of the group thus defined is substituted by one to three substituents selected from carboxy, esterified carboxy, halogen, nitro and oxo,

— alkanoylamino substituted by 9H-purinyl and phenyl, in which the bond between the 9H-purinyl and the alkane moiety is interrupted by one —S— and an optional carbon chain of the alkane moiety is interrupted by one —NH—, and further an optional carbon atom of the group thus defined is substituted by one oxo,

— alkanoylamino substituted by phenyl and thienyl, in which the bond between the phenyl and the alkane moiety is interrupted by one bivalent radical selected from —O— and —NH— and an optional carbon chain of the alkane moiety is interrupted by one —NH—, and further optional carbon atoms of the group thus defined are substituted by three substituents selected from esterified carboxy, halogen, nitro and oxo,

— alkanoylamino substituted by phenyl and pyridyl-1-oxide, in which the bond between the pyridyl-1-oxide and the alkane moiety is interrupted by one —S— and an optional carbon chain of the alkane moiety is interrupted by one —NH—, and further an optional carbon atom of the group thus defined is substituted by oxo,

— alkanoylamino substituted by naphthyl and phenyl, in which the bond between the naphthyl and the alkane moiety is interrupted by one bivalent radical selected from —O— and —NH— and an optional carbon chain of the alkane moiety is interrupted by one or two bivalent radicals selected from —O—, —S—, —NH— and



and further an optional carbon atom of the group thus defined is substituted by oxo,

— alkanoylamino substituted by phenyl and pyrimidinyl, in which the bond between the pyrimidinyl and the alkane moiety is interrupted by one —S— and an optional carbon chain of the alkane moiety is interrupted by one —NH—, and further optional carbon atoms of the group thus defined are substituted by one amino, one hydroxy and one oxo,

— triphenylalkanoylamino, in which the bond between the one or two phenyls and the alkane moiety is interrupted by one or two bivalent radicals selected from —O— and —NH— and an optional carbon chain of the alkane moiety is interrupted by one —NH—, and further an optional carbon atom(s) of the group thus defined is substituted by one or two substituents selected from halogen and oxo,

— alkanoylamino substituted by naphthyl and diphenyl, in which the bond between the naphthyl and the alkane moiety is interrupted by one —O— and an optional carbon chain of the alkane moiety is interrupted by one —NH—, and further an optional carbon atom of the group thus defined is substituted by oxo,

— alkanoylamino substituted by dinaphthyl and phenyl, in which the bond between the two npahthyl and the alkane moiety is interrupted by one —O— and an optional carbon chain of the alkane moiety is interrupted by one —NH—, and further an optional carbon atom of the group thus defined is substituted by oxo,

— phenylalkanoylamino, in which the bond between the phenyl and the alkane moiety is interrupted by one bivalent radical selected from —O—, —NH— and —S— and optional carbon chains of the alkane moiety are interrupted by one phenylene and one to three bivalent radicals selected from —O— and —NH—, and further an optional carbon atom(s) of the group thus defined is substituted by one to five substituents selected from carboxy, esterified carboxy, halogen, nitro, oxo, thioxo and hydroxyimino,

— naphthylalkanoylamino, in which the bond between the naphthyl and the alkane moiety is interrupted by one —NH— and optional carbon chains of the alkane moiety are interrupted by one phenylene and three bivalent radicals selected from —O— and —NH—, and further optional carbon atoms of the group thus defined are substituted by one carboxy, one oxo and one thioxo,

— alkanoylamino substituted by pyridyl and phenyl, in which the bond between the pyridyl and the alkane moiety is interrupted by one —S— and the optional carbon chains of the alkane moiety are interrupted by two phenylenes and three bivalent radicals selected from —O— and —NH—, and further optional carbon atoms of the group thus defined are substituted by four substituents selected from halogen and oxo,

— alkanoylamino substituted by phenyl and benzo[c]pyrrolidinyl, in which the bond between the phenyl and the alkane moiety is interrupted by one —NH— and an optional carbon chain(s) of the alkane moiety is interrupted by one phenylene and one —O—, and further optional carbon atoms of the group thus defined are substituted by five substituents selected from carboxy, esterified carboxy, nitro and oxo,

— diphenylalkanoylamino, in which the bond between the one or two phenyls and the alkane moiety is interrupted by one or two —NH— and an optional carbon chain(s) of the alkane moiety is interrupted by one phenylene and one to three bivalent radicals selected from —O— and —NH—, and further an optional carbon atom(s) of the group thus defined is substituted by one to five substituents selected from carboxy, nitro, esterified carboxy, oxo and thioxo,

— dinaphthylalkanoylamino, in which bonds between the two naphthyl and the alkane moiety are interrupted by one —NH— and optional carbon chains of the alkane moiety are interrupted by one phenylene and three bivalent radicals selected from —O— and —NH—, and further optional carbon atoms of the group thus defined are substituted by three substituents selected from carboxy and thioxo,

— alkanoylamino substituted by phenyl and thienyl, in which the bond between the thienyl and the alkane moiety is interrupted by one tetrazol-1,5-diyl and an optional carbon chain of the alkane moiety is interrupted by one —NH—, and further an optional carbon atom of the group thus defined is substituted by one oxo,

— phenylalkanoylamino, in which the bond between the phenyl and the alkane moiety is interrupted by one —O— and an optional carbon chain of the alkane moiety is interrupted by one —NH—, and further the optional carbon atoms of the group thus defined are substituted by one halogen, one nitro and one oxo,

— diphenylalkanoylamino, in which the bond between the phenyl and the alkane moiety is interrupted by one phenylene and one —O— and an optional carbon chain of the alkane moiety is interrupted by one —NH—, and further an optional carbon atom of the group thus defined is substituted by one oxo,

— diphenylalkanoylamino, in which the bond between the phenyl and the alkane moiety is interrupted by one isoxazol-3,4-diyl which is substituted by one alkyl and an optional carbon chain of the alkane moiety is interrupted by one —NH—, and

further an optional carbon atom of the group thus defined is substituted by one oxo,

— benzamido, in which the bond between the phenyl and the carbonyl is interrupted by isoxazol-3,4-diyl which is substituted by one alkyl, and further an optional carbon atom of the group thus defined is substituted by halogen,

— phenylalkanoylamino, in which the bond between the phenyl and the alkane moiety is interrupted by one bivalent radical selected from phenylene and 1,3,5-oxadiazol-2,4-diyl and one or two bivalent radicals selected from —O—, —NH— and —SO_2—, and further the optional carbon atom of the group thus defined may be substituted by one carboxy and one hydroxy,

— phenylalkanoylamino, in which the bond between the phenyl and the alkane moiety is interupted by one 4,5-dihydro-1,2,4-oxadiazol-3,4-diyl, and an optional carbon atom of the group thus defined is substituted by one oxo,

— thienylalkanoylamino, in which the bond between the thienyl and the alkane moiety is interrupted by 1H-tetrazol-1,5-diyl.

With respect to the compounds (I), (I'), (II), (XXXXV), (XXXXVI), (XXXXVII), (XXXXVIII), (XXXXXII), (XXXXXIII) and (XXXXXIV): Suitable examples of saturated or unsaturated normal (or branched) aliphatic hydrocarbon moeity in the definition for " A " may include alkyl which may be branched (e.g. methyl, ethyl, propyl, butyl, pentyl, isopropyl, 1-methylpropyl, isobutyl, tert-butyl, methylbutyl, methylpentyl, ethylpropyl, ethylbutyl, neopentyl, dimethylbutyl) and alkenyl, which may be branched, (e.g. 1-propenyl, allyl, 1-butenyl, 1-pentenyl, isopropenyl, methylpropenyl, methylbutenyl, methylpentenyl, ethylpropenyl, ethylbutenyl, dimethylpropenyl, dimethylbutenyl.

In this specification the term " lower ", when used to qualify organic radicals, means containing from 1 to 6 carbon atoms.

Suitable examples of the derivative of carboxy in saturated or unsaturated normal (or branched) aliphatic hydrocarbon residue which is substituted by at least one substituent of carboxy or the derivative of carboxy, cyano, hydroxy and amino may include an ester, an acid amide and a salt, and are exemplified as follows.

(a) Ester:

Esters are conventional ones, including silyl esters, aliphatic esters and esters containing an aromatic or a heterocyclic ring.

The suitable silyl esters may be illustrated by examples of a tri-(lower)alkylsilyl (e.g. trimethylsilyl, triethylsilyl) esters.

The suitable aliphatic esters may include saturated or unsaturated acyclic or cyclic aliphatic esters which may be branched or which may contain a cyclic ring, such as aliphatic esters, for example, alkyl (e.g. methyl, ethyl, propyl, isopropyl, 1-cyclopropylethyl, butyl, tert-butyl, octyl, nonyl, undecyl) esters; alkenyl (e.g., vinyl, 1-propenyl, allyl, 3-butenyl) esters; alkynyl (e.g., 3-butynyl, 4-pentynyl) esters; cycloalkyl (e.g., cyclopentyl, cyclohexyl, cycloheptyl) esters; and aliphatic esters containing at least one heteroatom of nitrogen, sulfur and oxygen atom, for example, lower alkoxyalkyl (e.g., methoxymethyl, ethoxyethyl, methoxyethyl) esters; lower alkanoyloxyalkyl (e.g., acetoxymethyl, propionyloxymethyl, pivaloyloxymethyl) esters; alkylthioalkyl (e.g., methylthiomethyl, ethylthioethyl, methylthiopropyl) esters; dialkylamino (e.g., dimethylamino, diethylamino, dipropylamino) esters; alkylideneamino (e.g., ethylideneamino, propylideneamino, isopropylideneamino) esters; lower alkylsulfinyl(lower)alkyl (e.g., methylsulfinylmethyl, ethylsulfinylmethyl) esters.

The suitable esters containing an aromatic ring may include, for example, aryl (e.g., phenyl, xylyl, tolyl, naphthyl, indanyl, dihydroanthryl) esters; aralkyl (e.g., benzyl, phenethyl) esters; aryloxyalkyl (e.g., phenoxymethyl, phenoxyethyl, phenoxypropyl) esters; arylthioalkyl (e.g., phenylthiomethyl, phenylthioethyl, phenylthiopropyl) esters; arylsulfinylalkyl (e.g., phenylsulfinylmethyl, phenylsulfinylethyl) esters; aryloxyalkyl (e.g., benzoylmethyl, toluoylethyl) esters; aryloylamino (e.g., phthalimido) esters.

The suitable esters containing an heterocyclic ring may include, for example, heterocyclic esters, heterocyclicalkyl esters; in which the suitable heterocyclic ester may include, for example, saturated or unsaturated, condensed or uncondensed 3 to 8-membered heterocyclic group containing 1 to 4 hetero-atom(s) such as an oxygen, sulfur and nitrogen atom (e.g., pyridyl, piperidino, 2-pyridon-1-yl, tetrahydropyranyl, quinolyl, pyrazolyl) esters; and the suitable heterocyclicalkyl esters may include, for example, saturated or unsaturated, condensed or uncondensed 3 to 8-membered heterocyclic containing 1 to 4 heteroatom(s) such as an oxygen, sulfur and nitrogen atom (e.g., pyridyl, piperidino, 2-pyridon-1-yl, tetrahydropyranyl, quinolyl, pyrazolyl)-substituted-alkyl (e.g., methyl, ethyl, propyl) esters;

The silyl esters, the aliphatic esters and the esters containing an aromatic or heterocyclic ring as mentioned above may have 1 to 10 appropriate substituent(s) such as lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl), lower cycloalkyl (e.g., cyclopropyl, cyclohexyl), lower alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy), lower alkylthio (e.g., methylthio, ethylthio, propylthio), lower alkylsulfinyl (e.g., methylsulfinyl, ethylsulfinyl, propylsulfinyl), lower alkanesulfonyl (e.g., methanesulfonyl, ethanesulfonyl), phenylazo, halogen (e.g., chlorine, bromine, fluorine), cyano, nitro, examples of which are illustrated by mono(or di or tri)-halo(lower)alkyl (e.g., chloromethyl, bromoethyl, dichloromethyl, 2,2,2-trichloroethyl, 2,2,2-tribromoethyl) esters, cyano(lower)alkyl (e.g., cyano methyl, cyanoethyl) esters, mono(or di or tri or tetra or penta)halophenyl (e.g., 4-chlorophenyl, 3,5-dibromophenyl, 2,4,5-trichlorophenyl, 2,4,6-trichlorophenyl, pentachlorophenyl) esters, lower alkanesulfonylphenyl (e.g., 4-methanesulfonylphenyl, 2-ethanesulfonylphenyl) esters, 2-(or 3 or 4-)phenylazophenyl esters, mono(or di or tri)nitrophenyl (e.g., 4-nitrophenyl, 2,4-dinitrophenyl, 3,4,5-trinitrophenyl) esters, mono(or di or tri or tetra or penta)halophenyl(lower)alkyl (e.g., 2-chlorobenzyl, 2,4-dibromobenzyl, 3,4,5-trichlorobenzyl, pentachlorobenzyl) esters, mono(or di or tri)nitrophenyl(lower)alkyl (e.g., 2-nitrobenzyl, 2,4-dinitrobenzyl, 3,4,5-trinitrobenzyl) esters, mono(or di or tri) (lower)-alkoxyphenyl(lower)alkyl (e.g., 2-methoxybenzyl, 3,4-dimethoxybenzyl, 3,4,5-trimethoxybenzyl) esters, hydroxy and di(lower)alkylphenyl(lower)alkyl (e.g., 3,5-dimethyl-4-hydroxybenzyl, 3,5-ditert-butyl-4-hydroxybenzyl, etc.) esters.

(b) Acid amide:

The suitable acid amides may include, for example, N-unsubstituted acid amide, N-lower alkyl acid amide (e.g., N-methyl acid amide, N-ethyl acid amide), N,N-di(lower)alkyl acid amide (e.g., N,N-dimethyl acid amide, N,N-diethyl acid amide, N-methyl-N-ethyl acid amide), N-phenyl acid amide, or an acid amide with pyrazole, imidazole, 4-lower alkylimidazole (e.g., 4-methylimidazole, 4-ethylimidazole.)

(c) Salt:

Suitable salts may include salt with inorganic base (e.g., sodium salt, potassium salt, magnesium salt, ammonium salt), and organic base (e.g., dicyclohexylamine salt, pyridine salt, ethanolamine salt).

With respect to the compound (IV):
Suitable examples of alkyl in the definition for " Y " may include those of " the alkyl which may be branched " as mentioned above.

Suitable examples of protected group in the protected amino or the protected hydroxy in the definition for " Y " may include a conventional acyl such as conventional alkanoyl (e.g., formyl, acetyl), conventional haloalkanoyl (e.g., dichloroacetyl, trifluoroacetyl), conventional aroyl (e.g., benzoyl), conventional alkoxycarbonyl (e.g., ethoxycarbonyl, tert-butoxycarbonyl, adamantyloxycarbonyl); conventional haloalkoxycarbonyl (e.g., trichloroethoxycarbonyl) or conventional substituted or unsubstituted aralkoxycarbonyl (e.g., benzyloxycarbonyl, p-nitrobenzyloxycarbonyl).

The protected groups as illustrated above are to be referred to a group attached to the terminal amino or hydroxy function in the acyl amino for R_1, and, for convenience sake to explain the present invention, the term " protected group is also referred, with the same meaning as explained above, to a group attached to the other terminal functional group i.e. carboxy group hereinafter used in the specification.

With respect to the compound (I'); (I''); and (III'):
Suitable examples of acyl in the acylamino for R_1' may include the same examples as illustrated for the acyl in the definition for R_1.

With respect to the compound (I''):
Suitable examples of groups for " A' " may include the same examples as illustrated for the groups in the definition for " A " excepting hydrogen.

With respect to the compounds (V), (VI), (VII), (XIII), (X), (XXI), (XXIX), (XXX), (XXXIII) and (XXXIV):

A suitable acyl moiety in the acylamino for R_2, R_5, R_8, R_{10}, R_{20}, R_{22}, R_{28}, R_{29}, R_{34}, R_{36} and R_{38} may include the same aliphatic acyl, aromatic acyl, heterocyclic acyl and aliphatic acyl whose aliphatic moiety is substituted by aromatic group or heterocyclic group as illustrated for the acyl in the acylamino for R_1.

Suitable examples of the above acyl may be:
alkanoyl or cycloalkanoyl (e.g., formyl, acetyl, propionyl, butyryl, isobutyryl, pivaloyl, cyclohexanecarbonyl); aralkanoyl (e.g., phenylacetyl, phenylpropionyl, naphthylacetyl); heterocyclic alkanoyl (e.g., thienylacetyl, tetrazolylacetyl, furylacetyl, thiadiazolylacetyl, thiazolylacetyl, morpholinoacetyl, piperazinoacetyl, benzothiazolyl-

acetyl, thienylpropionyl); aroyl (e.g., benzoyl, toluoyl, xyloyl, naphthoyl, phthaloyl); heterocyclic carbonyl (e.g., thenoyl, furoyl, prolyl, nicotinoyl, isonicotinoyl, benzodioxanecarbonyl) or cycloalkylalkanoyl (e.g. cyclopentylacetyl, cyclohexylacetyl).

In the above examples; the optional bond of the alkylene moiety, the bond between the carbonyl and the aliphatic, aromatic or heterocyclic group, and/or the bond between the alkylene and the cycloalkyl, aryl or heterocyclic group may be interrupted by a bivalent radical —O—, —S— or —NH—. Suitable examples of such acyl may be alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl); cycloalkoxycarbonyl (e.g. cyclopropoxycarbonyl, cyclohexyloxycarbonyl, bornyloxycarbonyl, adamantyloxycarbonyl); aralkoxycarbonyl (e.g., benzyloxycarbonyl, phenethyloxycarbonyl); heterocyclic alkoxycarbonyl (e.g., furfuryloxycarbonyl, pyrrolidinylmethoxycarbonyl, pyridylmethoxycarbonyl); aryloxycarbonyl (e.g., phenoxycarbonyl, naphthoxycarbonyl); alkoxythiocarbonyl (e.g., methoxythiocarbonyl, ethoxythiocarbonyl, propoxythiocarbonyl); alkoxyalkanoyl (e.g., methoxyacetyl, ethoxypropionyl); cycloalkoxyalkanoyl (e.g., cyclohexyloxyacetyl, bornyloxyacetyl, adamantyloxyacetyl); alkylthioalkanoyl (e.g., methylthioacetyl, ethylthioacetyl, isopropylthioacetyl, butylthioacetyl); arylthioalkanoyl (e.g., phenylthioacetyl); heterocyclicthioalkanoyl (e.g., thienylthioacetyl, thienylthiopropionyl, thiazolylthioacetyl, thiadiazolylthioacetyl, oxazolylthioacetyl, oxadiazolylthioacetyl, triazolylthioacetyl, tetrazolylthioacetyl, benzothiazolylthioacetyl); N-alkylcarbamoyl (e.g., N-methylcarbamoyl, N-ethylcarbamoyl); N-arylcarbamoyl (e.g., N-phenylcarbamoyl, N-naphthlycarbamoyl); N-alkylthiocarbamoyl (e.g., N-methylthiocarbamoyl, N-ethylthiocarbamoyl) and N-arylthiocarbamoyl (e.g., N-phenylthiocarbamoyl).

The optional carbon atom of said acyl group may be substituted by one or more suitable substituents such as a halogen atom (e.g., chlorine, bromine), nitro or formyl.

With respect to the compound (XI):

Suitable examples of acid residue in X_1 may include an acid residue of

an inorganic acid (e.g., hydrochloric, hydrobromic, hydroiodic, sulfuric acid),

an organic acid such as organic sulfonic acid (e.g., methanesulfonic, benzenesulfonic or toluenesulfonic acid), an organic carbamic acid (e.g., dimethylcarbamic or diethylcarbamic acid).

Suitable examples of bivalent aliphatic hydrocarbon radical in the definition for "A_1" may include alkylene or alkylidene (e.g., methylene, ethylene, trimethylene, propylene, pentylidene, hexamethylene), in which the optional carbon atom may be replaced by at least one radical selected from —NH—, —O—, and

and further may be substituted by oxo, aryl such as phenyl, naphthyl, or heterocyclic group such as thienyl.

With respect to the compound (XII):

Suitable examples of residue of nucleophile in the definition for R_{11} may include substituted or unsubstituted alkylthio (e.g., methylthio, ethylthio, propylthio, isopropylthio); alkenylthio (e.g., vinylthio, propenylthio, isopropenylthio, butenylthio); alkynylthio (e.g., 2-propynylthio); arylthio (e.g., phenylthio, naphthylthio);

substituted or unsubstituted aralkylthio (e.g., benzylthio, phenethylthio, phenylpropylthio, phenylbutylthio), in which the optional carbon atom of said alkyl moiety may be replaced by at least one radical selected from —O—, —NH— and further may be substituted by oxo;

substituted or unsubstituted heterocyclicthio (e.g., morpholinylthio, thiadiazolylthio, oxadiazolylthio, triazolylthio, pyrimidinylthio, oxazolylthio, tetrazolylthio, purinylthio, pyridin-1-oxide-2-ylthio, 5-methyl-1,3,4-thiadiazolylthio, 5-ethyl-1,3,4-thiadiazolylthio, 1-methyltetrazolylthio, 2-aminothiazolylthio, 1-methyltriazolylthio); substituted or unsubstituted aryloxy (e.g., phenoxy, tolyloxy, chlorophenoxy, biphenylyloxy, naphthoxy, methoxyphenoxy, phenoxyphenoxy, vinylphenoxy, propenylphenoxy, acetylphenoxy, benzoylphenyloxy, benzoylnaphthoxy);

substituted or unsubstituted arylamino (e.g., anilino, N-methylanilino, naphthylamino);

substituted or unsubstituted aralkylamino (e.g., benzylamino N-methylbenzylamino, phenethylamino).

In the above, the residue of nucleophile may be substituted by at least one substituent selected from carboxy, esterified carboxy (e.g., methoxycarbonyl, ethoxycarbonyl,

propoxycarbonyl), halogen (e.g., bromine, chlorine), nitro, formyl amino, hydroxy, protected amino or protected hydroxy.

With respect to compounds (XIII) and (XIV):

Suitable example of acyl moiety is an acyl having protected amino, protected hydroxy and/or protected carboxy for R_{12} may include the same examples as defined and illustrated for the acyl in the acylamino for R_1.

Suitable example of acyl moiety of an acyl having amino, hydroxy or carboxy function in R'_{12} may include the same examples as defined and illustrated for the acyl in the acylamino for R_1.

Suitable examples of alkyl in the definition for R_{13} may include methyl, ethyl and propyl.

Suitable halogen in the definition for X_2 may include bromine and chlorine.

With respect to compounds (XV) and (XVI):

Suitable examples of acyl for R_{14} may include the same examples as defined and illustrated for the acyl in the acylamino for R_1, and more particularly aroyl (e.g., benzoyl, naphthoyl), aralkanoyl (e.g., phenylacetyl, phenylpropionyl); heterocyclic alkanoyl such as thienylalkanoyl (e.g., thienyl acetyl, thienylpropionyl, thienylbutyryl); an alkoxyaralkanoyl, in which the optional carbon atom is substituted by at least one substituent selected from hydroxyimino, carboxy, amino and protected amino, the examples of which are illustrated as follows.

2-[4-(3-carboxy-3-acetamidopropoxy)phenyl]-2-hydroxyiminoacetyl,

2-[4-{3-carboxy-3-(3-phenylureido)propoxy}phenyl]-2-hydroxyiminoacetyl,

2-[4-{3-(2,2,2-trifluoroacetamido)-3-carboxypropoxy}phenyl]-2-hydroxyiminoacetyl.

Suitable examples of halogen for X_3 and X_4 may be the same as illustrated for the halogen for X_2.

With respect to the compound (XVII) and (XVIII):

Suitable examples for the definition for R_{16} are as follows:

aryl (e.g., phenyl, naphthyl);

alkyl (e.g., methyl, ethyl, propyl);

aralkyl (e.g., benzyl, phenylpropyl);

aryloxy (e.g., phenoxy, naphthoxy);

heterocyclic group (e.g., thienyl, pyranyl, 5,6-dihydro-2H-pyranyl, isobenzofuranyl, indolyl);

heterocyclicalkyl (e.g., thienymethyl, thienylpropyl, furylmethyl, furylethyl, furylpropyl, indolylethyl, thiadiazolylmethyl, thiadiazolylethyl, oxazolylmethyl).

Suitable examples of hydrocarbon residue having amino in the definition for R_{16} may include aminoalkyl (e.g., aminomethyl, aminoethyl, aminopropyl), and aminoaryl (e.g., aminophenyl, aminonaphthyl).

Suitable examples for the definition for R_{17} are as follows.

Hydrocarbon group in acylamino-substituted-hydrocarbon residue for R_{17} may include alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl, hexyl); alkenyl (e.g., vinyl, propenyl, isopropenyl); aryl (e.g., phenyl, naphthyl); aralkyl (e.g., benzyl, phenethyl, phenylpropyl, phenylbutyl), and the optional carbon atom of said hydrocarbon group may be substituted by at least one substituent selected from halogen (e.g., bromine, chlorine), hydroxy and carboxy, and further the optional carbon atom of said hydrocarbon group may be replaced by at least one bivalent radical selected from oxygen, nitrogen, sulfur, imino, carbonyl, thiocarbonyl and carbamoyl.

And, suitable examples of acyl in acylamino and acylamino-substituted-hydrocarbon residue for R_{17} are the same as defined and illustrated for the acyl in the acylamino for R_1.

With respect to compounds (XIX) and (XX):

Suitable examples of aryl for R_{18} may be the same as mentioned above.

Suitable examples of alkyl and aryl for R_{19} may be the same as mentioned above.

Suitable examples of N-arylcarbamoylalkyl for R_{19} may include N-phenylcarbamoylmethyl, N-phenylcarbamoylethyl, N-naphthylcarbamoylmethyl and N-naphthylcarbamoylethyl.

With respect to the compound (XXII):

Suitable examples of " aryl substituted by at least one substituent of nitro and esterified carboxy " for R_{21} may include p-nitrophenyl, 2,4-dinitrophenyl and 2-nitro-4-methoxycarbonylphenyl, and suitable examples of substituted aryl moiety in arylamino whose aryl ring is substituted by at least one substituent of nitro and esterified carboxy for R_{22} may be the same as illustrated for the definition for R_{21}.

With respect to the compound (XXIV):

Suitable examples of mono- or di-alkylamino for R_{23} may include mono-alkylamino such as methylamino, ethylamino, propylamino, isopropylamino, butylamino and dialkyl-

amino such as dimethylamino diethylamino, and the optional carbon atom of said mono- or di-alkylamino may be substituted by esterified carboxy such as alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl).

With respect to the compound (XXV):

Suitable examples of nitroaryl for R_{24} may include mono- or di-nitrophenyl or mono or dinitronaphthyl.

With respect to the compound (XXVI):

Suitable examples of aminoaryl for R_{25} may include mono or diaminophenyl or mono or diaminonaphthyl.

With respect to compounds (XXVII) and (XXVIII):

Suitable examples of aryl for R_{26} may include phenyl and naphthyl.

A suitable example of bivalent aliphatic hydrocarbon radical for " A_2 " is the same as illustrated in the definition for " A_1 ".

Suitable examples of halogen atom for X_5 may include bromine and chlorine.

Suitable examples of alkoxy for R_{27} may include methoxy, ethoxy, propoxy, whose alkyl moiety may be substituted by suitable substituent such as carboxy and esterified carboxy, for example, carboxymethoxy, methoxycarbonylmethoxy.

Suitable examples of alkanoylamino for R_{27} may include formamido, acetamido, propionamido), whose alkyl moiety may be substituted by ammonio radical (e.g., N,N,N-trimethylammonio, N,N,N-triethylammonio or pyridinio) which bears an anion such as chloro, bromo, iodo, sulfoxy, methylsulfoxy, ethylsulfoxy, formyloxy or p-toluenesulfonyloxy.

With respect to the compound (XXXII):

A suitable example of alkyl for R_{32} and R_{33} is the same as illustrated for the alkyl for R_{13}.

With respect to the compounds (XXXIII) and (XXXIV):

A suitable example of alkyl for R_{39}, R_{40} and R_{41} and alkyl moiety in alkoxy and acyloxyalkoxy for R_{38} is the same as illustrated for the alkyl for R_{13}.

Suitable examples for acyl moiety in acyloxyalkoxy for R_{38} is a conventional alkanoyl (e.g. acetyl, propionyl, butyryl, isobutyryl, pivaloyl) as illustrated for the protected group for Y.

Suitable examples of substituted-alkyl in the definitions for R_{39} and R_{41} may include acyloxyalkyl such as alkanoyloxyalkyl (e.g., acetoxymethyl, acetoxyethyl, acetoxypropyl, propionyloxymethyl, propionyloxyethyl, butyryloxymethyl, pivaloyloxymethyl) and haloalkyl such as monohaloalkyl (e.g., fluoromethyl, chloromethyl, bromomethyl, chloroethyl, bromoethyl, chloropropyl, bromopropyl), dihaloalkyl (e.g. dichloroethyl, 2,3-dichloropropyl) and trihaloalkyl (e.g. trichloromethyl).

With respect to the compounds (XXXV) and (XXXVI):

Suitable aryl in the definition for R_{42} may include aryl which may be substituted by suitable substituent such as carboxy, the examples of which are phenyl, carboxyphenyl, tolyl and naphthyl.

A suitable example of alkylene for " A_3 " may include methylene, ethylene, propylene.

With respect to the compounds (XXXIX) and (XXXX):

Suitable examples of aryl substituted by at least one substituent of nitro and esterified carboxy for R_{43} are the same as illustrated for the same group for R_{31}.

Suitable examples of aromatic heterocyclic group for R_{43} may include the same as illustrated in the explanation of the heterocyclic group for R_1 of the compound (1), and the more particular examples thereof are pyridyl, pyridyl-1-oxide, pyrimidynyl, oxadiazolyl which may be substituted by an aryl such as phenyl, tolyl or naphthyl.

With respect to the compounds (XXXXI) and (XXXXII):

Suitable examples of aralkyl for R_{44} are the same as illustrated for R_{15}.

Suitable examples of alkyl for R_{45} and R_{46} are the same as illustrated for R_{13}.

With respect to the compounds (XXXXIII) and (XXXXIV):

Suitable examples of " carboxy or its derivative " for R_{47} are the same as illustrated in the explanation for " A ", i.e. that of " carboxy or its derivative ".

Suitable examples of protected group in the protected amino for R_{48} may include the same as illustrated in the explanation for Y.

With respect to the compounds (XXXXV), (XXXXVI), (XXXXVII), (XXXXVIII), (XXXXIX), (XXXXXII), (XXXXXIII) and (XXXXXIV):

Suitable examples of acyl moiety in the acylamino group in the definition for R_{40}, R_{50}, R_{51}, R_{52}, R_{53}, R_{54}, R_{55} and R_{56} may include the same as illustrated in the explanation of an acyl moiety in the acylamino for R_1.

Suitable examples of " carboxy or its reactive derivative " moiety in the definition

for R_{49} are the same as illustrated in explanation of " A ", i.e. that of " carboxy or its derivative.

Suitable examples of " N-(hydroxyalkyl)carbamoyl " moiety in the definition for R_{50} may include N-(hydroxymethyl)carbamoyl, N-(hydroxyethyl)carbamoyl, N-(hydroxypropyl)carbamoyl.

Suitable examples of " N-aralkylcarbamoyl " moiety in the definition for R_{51} may include N-benzylcarbamoyl, N-phenethylcarbamoyl, in which aryl moiety may be substituted by suitable substituent(s).

Suitable examples of the ester in " esterified carboxyalkylamino " moiety in the definition for R_{52} may include the same as illustrated in the explanation for " A ", i.e. that of " ester ", and more particularly are methoxycarbonylethylamino, ethoxycarbonylethylamino, and propoxycarbonylmethylamino.

Suitable examples of " alkenyl substituted by esterified carboxy " in the definition for R_{53} may include an alkoxycarbonyl alkenyl such as methoxycarbonylvinyl, methoxycarbonylpropenyl, ethoxycarbonylvinyl, methoxycarbonyl-1-methylvinyl, ethyoxycarbonyl-2-propenyl, and further examples of the ester in " esterified carboxy " moiety may include the same as illustrated in the explanation for " A ", i.e. that of " ester ".

Suitable examples of alkanoyl in the definition for R_{55} may include the same as illustrated in the explanation of an acyl moiety in the acylamino for R_1.

Suitable examples of aroyl moiety in the definition for R_{55} may include the same as illustrated in the explanation of acyl moiety in the acylamino for R_1.

Suitable examples of alkyl moiety in the definition for R_{56} is the same as illustrated for R_{13}.

Suitable examples of α-hydroxy aralkyl moiety in the definition for R_{56} may include α-hydroxybenzyl, 1-hydroxy-1-(1-naphthyl)methyl.

With respect to the compound (XXXXXVI):

Suitable examples of aralkyl moiety in aralkylamino for R_{57} may include the same as illustrated for R_{15}.

With respect to the compounds (XXXXXVI) and (XXXXXVII):

Suitable examples of halogen for X_8 may include the same as illustrated in the definition for X_2.

Suitable examples of alkyl for R_{58}, R_{59} and R_{60} are the same as illustrated for R_{13}.

With respect to the compound (XXXXXI):

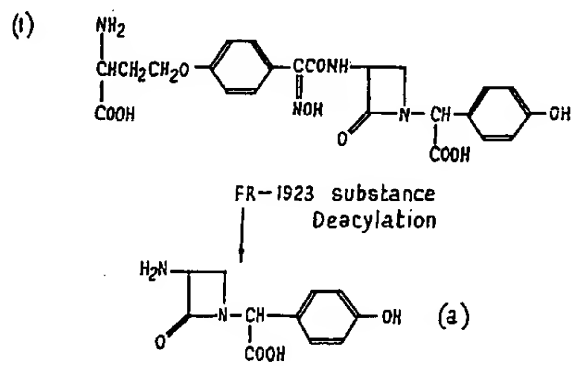
Suitable examples of aralkanoyl moiety in aralkanoylamino for R_{61} may include the same as illustrated in the explanation of the acyl moiety in the acylamino for R_1.

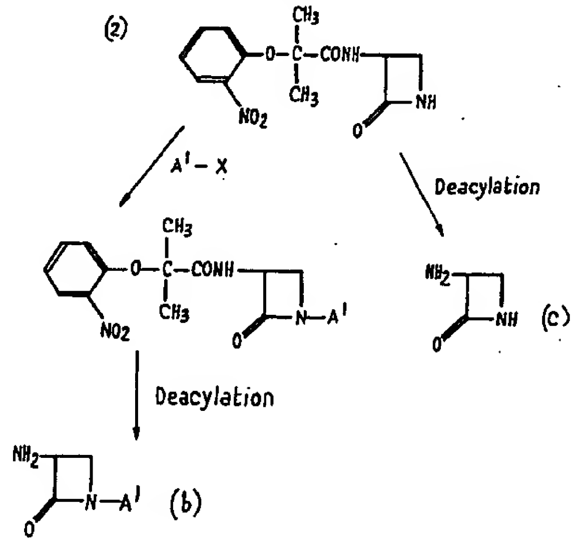
The processes of the present invention are explained in details hereinafter.

In the present invention, as key starting compounds, there are employed FR—1923 substance and 1-substituted-3-amino-2-azetidinone (a) which can be derived from FR—1923 substance; and 1-substituted-3-amino-2-azetidinone (b) and 3-amino-2-azetidinone (c) which can be derived from 3-acylamino-2-azetidinone.

Such starting compounds can be prepared, for example, by processes as shown in the following scheme.

(1)





wherein X is an acid residue and A′ is as defined above.

(1) Process 1: (II)→(I′)

In this process, the object compound (I′) can be prepared by reacting the compound (II) or its reactive derivative at the amino with an acylating agent.

As acylating agents to be used in the present reaction, there may be exemplified an organic carboxylic acid, an organic sulfonic acid and the corresponding thio-, or imido-acid, and more particularly, an aliphatic acid, an aromatic or heterocyclic carboxylic acid, and the corresponding sulfonic acid, carbamic acid, carbonic acid and thio-acid, and their reactive derivative.

As the reactive derivatives, there may be exemplified an acid anhydride, an activated amide, an activated ester, an isocyanate and an isothiocyanate.

Exmples of such reactive derivatives are illustrated by an acid azide;

an mixed acid anhydride with an acid such as dialkylphosphoric acid, phenylphosphoric acid; diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, hydrohalogenic acid (e.g., hydrochloric acid, hydrobromic acid), sulfuric acid, monoalkyl carbonic acid, aliphatic carboxylic acid (e.g., acetic acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid or trichloroacetic acid), aromatic carboxylic acid (e.g., benzoic acid), or symmetrical acid anhydride;

an acid amide with pyrazole, imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; and

an ester (e.g., cyanomethyl ester, methoxymethyl ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, methanesulfonylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, or ester with N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide or N-hydroxyphthalimide).

The above reactive derivatives are selected according to the kind of the acid to be used. In the reaction, when free acid is used as an acylating agent, the reaction may be preferably conducted in the presence of a condensing agent such as N,N′-dicyclohexylcarbodiimide, N-cyclohexyl-N′-morpholinoethylcarbodiimide, N-cyclohexyl-N′-(4-diethylaminocyclohexyl)carbodiimide, N,N′-diethylcarbodiimide, N,N′-diisopropylcarbodiimide, N-ethyl-N′-(3-dimethylaminopropyl)carbodiimide, N,N′-carbonyldi-(2-methylimidazole), pentamethyleneketene-N-cyclohexylimide, diphenylketene-N-cyclohexylimine, alkoxyacetylene, 1-alkoxyl-1-chloroethylene, trialkyl phosphite, ethyl polyphosphate, isopropyl polyphosphate, phosphorus oxychloride, phosphorus trichloride, thionylchloride, oxalyl chloride, triphenylphosphine, 2-ethyl-7-hydroxybenzisoxazolium salt, 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide(chloromethylene)-dimethylammonium chloride, 2,2,4,4,6,6-hexachloro-2,2,4,4,6,6-hexahydro-1,3,5,2,4,6-triazatriphosphorine, or a mixed condensing agent such as triphenylphosphine and a carbon tetrahalide (e.g., carbon tetrachloride, carbon tetrabromide).

The example of an acyl group to be introduced into the amino group in the compound (I′) by the above acylating agent may be a dehydroxylated group of an aliphatic, aromatic and heterocyclic carboxylic acid, and the corresponding sulfonic acid, carbonic acid, carbamic acid and thio acid, and more particular acyl group may be the same acyl group as illustrated in the explanation of the acyl group in the acylamino group for R_1.

As the reactive derivative at the amino at the 3rd position of the compound (II), there may be exemplified Schiff's base, salt with acid (e.g. hydrochloric acid) and the conventional reactive derivative.

The acylation in the present process is conducted in a conventional manner known skilled in the art, for example, the acylation of 6-aminopenicillanic acid or 7-aminocephalosporanic acid to provide the corresponding 6-acylamino penicillin or 7-acylaminocephalosporin compounds.

That is, the present reaction is conducted by reacting the compound (II) or its reactive derivative at the amino with an acylating agent usually in a solvent which does not give bad influence to the reaction, for example, water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, dichloroethane, tetrahydrofuran, ethyl acetate, dimethylformamide, pyridine, and the hydrophilic solvent as mentioned above can be used in a mixture with water.

The present reaction can also be carried out in the presence of a base such as inorganic base (e.g., alkali metal bicarbonate) and an organic base such as trialkylamine (e.g., trimethylamine, triethylamine, tributylamine), N-methylmorpholine, N-methylpiperidine, N,N-dialkylaniline (e.g., N,N-dimethylaniline, N,N-diethylaniline), N,N-dialkylbenzylamine (e.g., N,N-diethylbenzylamine), pyridine, picoline, lutidine, 1,5-diazabicyclo[4,3,0]non-5-ene, 1,4-diazabicyclo[2,2,2]octane, 1,8-diazabicyclo[5,4,0]-undecene-7.

In the present reaction, a liquid base or liquid condensing agent also can be used as a solvent for the reaction.

There is no limitation to the present reaction temperature, and the present reaction can be preferrably carried out under cooling or at ambient temperature.

(2) Process 2: (III)→(I″)

In this process, the object compound (I″) can be prepared by reacting the compound (III) with a reagent of the formula: A′—X wherein A′ is as defined above and X is an acid residue.

In the reagent of the formula: A′—X, examples of the definitions for A′ are the same as illustrated in the explanation of the definitions for A excepting hydrogen. As examples of the acid residue for X, there may be exemplified an acid residue of an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid); an acid residue of an organic acid such as organic sulfate (e.g. methyl sulfate, ethyl sulfate), organic sulfonic acid (e.g. methane sulfonic acid, benzene sulfonic acid, toluene sulfonic acid) and organic carbamic acid (e.g. dimethylcarbamic acid, diethylcarbamic acid) and the like.

The reaction is usually conducted in a solvent. Suitable examples of the solvents are water, acetone, dioxane, acetonitrile, methylene chloride, chloroform, dichloroethane, tetrahydrofuran, ethyl acetate, dimethylformamide, pydridine, among which hydrophilic solvent can be used in a mixture with water. Any other solvent which does not give bad influence to the reaction also may be used.

There is no limitation to the reaction temperature, and the reaction is usually conducted at ambient temperature or under cooling.

In case that the compound (I″) thus produced has the derivative of carboxy or the protected carboxy as substituent, the compound (I″) may be subjected to elimination reaction, whereby said derivative of carboxy or protected group is converted into the corresponding carboxy group, whose reaction is also included within the scope of the present invention.

The elimination reaction is conducted by a conventional method, that is substantially the same methods as those explained in the elimination reaction for the hereinafter mentioned Process 3, e.g. solvolysis, reduction.

(3) Process 3: (I′)→(II)

In this process, the object compound (II) can be prepared by eliminating the acyl group of compound (I′) in a conventional manner.

A suitable method to be used in the elimination reaction of the acyl moiety in acylamino may include solvolysis such as hydrolysis using an acid or a base; hydrazinolysis and reduction such as chemical reduction or catalytic reduction and combined method comprising iminohalogenation, iminoetherification and solvolysis.

In the above reaction, suitable examples of reagents to be used are as follows.

For solvolysis:

Solvolysis is conducted in the presence of an acid or base.

Suitable acids are an inorganic acid (e.g. hydrochloric acid, sulfuric acid), an organic acid (e.g., formic acid, acetic acid, trifluoroacetic acid, propionic acid, benzenesulfonic acid, p-toluenesulfonic acid) or an acidic ion exchange resin.

Suitable bases are an inorganic base such as a hydroxide, carbonate or bicarbonate of an alkali metal (e.g., sodium, potassium), an alkaline earth metal (e.g., magnesium, calium), and the like, an organic base such as an alkoxide of the above metal, a tertiary amine such as trialkylamine (e.g., trimethylamine, triethylamine), a disubstituted arylamine (e.g., N,N-dimethylamine) or a heterocyclic amine (e.g., N-methylmorpholine, N-methylpiperidine, N,N-dimethylpiperazine, pyridine) or a basic ion exchange resin.

For reduction:

Reduction is conducted with a conventional chemical reducing agent or by conventional catalytic reduction.

Suitable reducing agents are a metal (e.g., tin, zinc, iron) or a combination of metalic compound (e.g., chromium chloride, chromium acetate) and an organic or an inorganic acid (e.g., acetic acid, propionic acid, hydrochloric acid).

Suitable catalysts used in catalytic reduction are conventional ones such as platinum catalysts (e.g., platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide or platinum wire), palladium catalysts (e.g., spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate or palladium on barium carbonate), nickel catalysts (e.g., reduced nickel, nickel oxide or Raney nickel), cobalt catalysts (e.g., reduced cobalt or Raney cobalt), iron catalysts (e.g., reduced iron or Raney iron) copper catalysts (e.g., reduced copper, Raney copper or Ullman copper), or other conventional catalysts.

For combined method:

Iminohalogenation, iminoetherification, and solvolysis are conducted with a conventional iminohalogenating agent and conventional iminoetherizing agent, and then by conventional solvolysis:

Suitable iminohalogenating agents are a phosphorus compound such as phosphorus trichloride, phosphorus pentachloride, phosphorus tribromide, phosphorus pentabromide, phosphorus oxychloride, and their reaction equivalents such as thionyl chloride or phosgene.

Suitable iminoetherifying agents used in the reaction with the resultant product in the foregoing iminohalogenation of the acylamino compound (I') are an alcohol such as an alkanol (e.g., methanol, ethanol, propanol, isopropanol, butanol, tert-butanol) or the corresponding alkanol having alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, buthoxy) as substituent(s) at the alkyl moiety thereof, and an alkoxide of such metal as mentioned above (e.g., sodium alkoxide, potassium alkoxide, calcium alkoxide, barium alkoxide), each of which is derived from said alcohol. Thus obtained reaction product is, if necessary, solvolyzed in a conventional manner.

The elimination reactions, i.e. solvolysis, hydrazinolysis, reduction and combined method comprising iminohalogenation, iminoetherification and solvolysis are conventional ones employed for the elimination of acyl group in acylamino group of penicillin and cephalosporin compounds, and said reactions may be conducted in the similar conditions to that of the elimination reaction in the penicillin and cephalosporin cases.

For example, the iminohalogenation and iminoetherification reactions are preferably conducted at ambient temperature or under cooling, and the solvolysis proceeds simply pouring the reaction mixture to water or a mixture of a hydrophilic solvent such as alcohol (e.g. methanol, ethanol) and water, and if necessary, with addition of an acid or base as exemplified above thereto.

The object compound (II) prepared in the above elimination reaction is also used as a key intermediate for the compound (I) of the present invention. That is, the introduction of an acyl group different from that of the compound (I') to 1-substituted-3-amino-2-azetizinone (II) can produce a new 1-substituted-3-acylamino-2-azetizinone (I) having different antimicrobial activity spectrum from that of the compound (I').

(4) Process 4: (IV)→(III')

The object compound (III') can be prepared by subjecting the compound (IV) to degradative elimination reaction.

Suitable methods to be used in this elimination reaction are a conventional solvolysis such as hydrolysis (e.g., an acidic or a basic hydrolysis) and a reduction (e.g., chemical or catalytic, reduction), which may be optionally selected depending on a kind of a starting compound (IV).

Solvolysis such as hydrolysis is conducted preferably in the presence of an acid or a base in a conventional manner, the examples of which are the same as those illustrated in the explanation of Process 3 and to be referred to them.

Suitable examples of reducing agents for chemical reduction and catalysts for catalytic reduction are also the same as those illustrated in the explanation of Process 3, and to be referred to them.

The degradative reduction is usually conducted by reducing the compound (IV) with a reducing agent in a solvent in a conventional manner. The reaction conditions, for example, the solvent to be used and the reduction temperature are selected in accordance with the reduction method used and/or the kind of the compounds (IV) and/or (III'). Generally, in the catalytic reduction method, it is preferable to employ a solvent such as methanol, ethanol, propanol, isopropanol or ethyl acetate. In the method using a combination of a metalic compound and an acid, said acid is generally used as a solvent, but if necessary, there is employed a solvent such as water or acetone.

The reaction temperature is not especially limited, and the reaction is usually conducted under cooling, at temperature or at an elevated temperature.

The object compound (III') as prepared above is also used as a key intermediate for the compound (I') of the present invention.

(5) Process 5: (V)→(VI)

In this process, the object compound (VI) is prepared by hydrolyzing the compound (V) or its derivative at carboxy. Examples of the derivative of carboxy of the starting compound is the same as illustrated in the explanation for the " A " of compound (I).

The hydrolysis is conducted in a conventional manner.

That is, a suitable method to be used in this hydrolysis is conducted in the presence of an acid or base, example of which is the same one as that illustrated in the hydrolysis in the explanation for Process 3.

Though there is no limitation to the reaction temperature, it may be suitably selected according to the hydrolyzing condition to be used in the reaction, and the reaction is preferably conducted at ambient temperature or at somewhat elevated temperature in accordance with the kind of the solvent of other reagent used.

(6) Process 6: (VII)→(VIII)

In this process, the object compound (VIII) can be prepared by reducing the compound (VII) or its derivative at carboxy.

Examples of the derivative at carboxy of the starting compound (VII) are the same as those illustrated in the explanation for " A " of the compound (I).

In this reduction, the reaction is conducted by a conventional method such as a catalytic reduction; a reduction using a combination of a metal such as iron, tin or zinc and an acid such as an inorganic acid (hydrochloric acid or sulfuric acid) or an organic acid (e.g. acetic acid); a combination of an alloy (e.g., sodium amalgam, aluminum amalgan) a metal (e.g., zinc, tin, iron), or a salt thereof (e.g., zinc chloride, stannous chloride, ferric or ferrous chloride) and water, an alkali solution or an alcohol (e.g., methanol, ethanol, propanol or butanol); a hydrazine compound (e.g., phenyl hydrazine or hydrazine); a combination of titanium chloride and hydrochloric acid; an alkali borohydride such as sodium borohydride, and potassium borohydride; diborane; or an electrolytic reduction.

Suitable examples of catalysts for the catalytic reduction are the same one as those illustrated in the explanation of the catalyst for Process 3.

The reaction conditions for this reduction, for example, the solvent to be used and the reaction temperature may optionally be selected in accordance with the reduction method to be used. In general, it is preferable to employ a solvent such as water, an alcohol as mentioned above, dioxane, acetonitrile, tetrahydrofuran, dimethylformamide or pyridine, and further the acid as mentioned above may also used as a solvent.

The reaction temperature is not especially limited, and the reaction is usually conducted under cooling, at ambient temperature or at an elevated temperature.

(7) Process 7: (IX)→(X)

In this process, the object compound (X) can be prepared by reacting the compound (IX) or its derivative at carboxy with an acylating agent.

Examples of the derivative at carboxy of the starting compound are the same as those illustrated in the explanation for " A " of the compound (I).

As acylating agents in the present reaction, there may be exemplified the same examples as those illustrated in the explanation of the acylating agents for Process 1.

The reaction conditions, for example, the solvent to be used and the reaction temperature are also substantially the same as those explained in the acylation for Process 1.

The present acylation may include, within its scope, the case that when the starting compound (IX) has group(s) of free hydroxy and hydroxyimino, it (they) is also occasionally acylated.

(8) Process 8: (XI)→(XII)

In this process, the object compound (XII) can be prepared by reacting the compound (XI) or its reactive derivative at carboxy with a nucleophile of the formula: R_{11}—H wherein R_{11} is residue of nucleophile, or its salt.

The nucleophile of the formula: R_{11}—H wherein R_{11} is as defined above to be used as a reagent may include an amine such as a primary and secondary amine, a thiol compound and a hydroxy compound, respectively.

Examples of the residue of nucleophile are aliphatic hydrocarbon amino (e.g. alkylamino, alkenylamino), di-aliphatic hydrocarbon amino (e.g. di-alkylamino), aromatic amino (phenylamino, tolylamino, naphthylamino), heterocyclic amino (thienylamino, thiadiazolylamino, triazolylamino), and aliphatic hydrocarbon-amino substituted by such aromatic or heterocyclic group; and aliphatic hydrocarbon thio(or oxy), aromatic thio (or oxy), heterocyclic thio (or oxy), and aliphatic hydrocarbon thio (or oxy) substituted by such aromatic or heterocyclic group; in which aliphatic hydrocarbon moiety may be saturated or unsaturated and branched or partially cyclized, and such aliphatic hydrocarbon moiety, aromatic ring and heterocyclic ring may be substituted by at least one possible substituent.

Suitable examples of aliphatic hydrocarbon residue, aromatic group, a heterocyclic group, aliphatic hydrocarbon residue substituted by aromatic or heterocyclic group may include the same ones as illustrated in the explanation of the definitions for R_1.

More suitable examples of the residue of nucleophile are illustrated in the explanation for the compound (XII).

In the present process, there may be employed the nucleophile for above thiol or phenolic hydroxy compound in a form of a salt such as an alkali metal (e.g., sodium, potassium) salt and an alkaline earth metal (e.g., magnesium, calcium) salt. In the case that the thiol compound has a free amino as substituent, said amino substituted thiol compound may be employed in the form of the salt of amino with an acid such as an inorganic acid (e.g., hydrochloric acid, hydrobromic acid) and an organic acid (formic acid, p-toluenesulfonic acid).

The reaction is usually conducted in an solvent. Suitable examples of the solvents include any solvent which does not give bad influence to the reaction, and are water, acetone, methanol, ethanol, tetrahydrofuran, dioxane, dimethylformamide, methylene chloride, chloroform, carbon tetrachloride, in which a hydrophilic solvent may be employed in a mixture with water.

The present reaction is preferably conducted in the presence of a base such as an alkalimetal hydroxide (e.g., sodium hydroxide, potassium hydroxide), an alkaline earth metal hydroxide (e.g., magnesium hydroxide, calcium hydroxide), an alkali metal carbonate (e.g., sodium carbonate), an alkaline earth metal carbonate (e.g., calcium carbonate), an alkali metal alkoxide (e.g., sodium alkoxide, potassium alkoxide), an alkaline earth metal alkoxide (e.g., calcium alkoxide, barium alkoxide), an organic amine (e.g., trimethylamine), a basic ionexchange resin.

There is no limitation to the present reaction temperature, and the reaction is usually carried out under cooling, at ambient temperature or at an elevated temperature.

(9) Process 9: (XIII)→(XIV)

In this process, the object compound (XIV) can be prepared by removing the protected group at the terminal amino, hydroxy and/or carboxy group in the acylamino group at the 3rd position of the compound (XIII) or its derivative at carboxy.

Examples of protected groups at the terminal amino, hydroxy and carboxy are the same as those illustrated in the explation of a protected group for the compound (IV), including the examples of ester of the carboxy group (i.e., esterified carboxy) as illustrated in the explanation of the derivative of carboxy for the compound (I).

Suitable methods to be used in the present reaction are conventional ones, including a conventional solvolysis, a convention reduction, a conventional method using a heavy metal, which are selected depending on a kind of a starting compound (XIII).

A solvolysis and reduction may be conducted in substantially the same manner illustrated in the explanation of the degradative elimination process for Process 4.

Suitable examples of heavy metal in the method using a heavy metal are copper, zinc.

Although there is no specific limitation to the reaction temperature and a preferable temperature are employed depending on a kind of the protecting group to be removed and the method to be used, the reaction is usually carried out under cooling, at ambient temperature or at somewhat elevated temperature.

By the present reaction, the protected group at the terminal amino, hydroxy and/or carboxy group in the acylamino group at the 3rd position of the starting compound (XIII) are removed to provide the corresponding free amino, hydroxy and/or carboxy, respectively, and when the derivative at carboxy in the substituent at the 1st position of the starting compound (XIII) are the ester, said ester is also converted into the corresponding free carboxy, which is also included within the scope of the present process.

(10) Process 10: (XV)→(XVI)

In this process, the object compound (XVI) can be prepared by reacting the compound (XV) or its derivative at carboxy with a halogenating agent.

Examples of the derivative at carboxy of the starting compound (XV) are the same as those illustrated in the explanation for the compound (II).

Suitable examples of halogenating agents may include halogen such as chlorine bromine; hypohalogenous acid or its alkyl ester such as hypochlorous acid, tert-butylhypochlorite, N-halamide such as N-bromoacetamide, N-iodoacetamide, N-bromosuccinamide, N-chlorosuccinimide, N-chlorophthalimide; a cuprous halogenide such as cuprous chloride, cuprous bromide; and, pyridinium hydrobromide perbromide or dioxane dibromide.

The reaction is usually carried out in an inert solvent.

A suitable solvent to be used in this reaction may include any solvent which does not bad influence to the reaction, for example, water, methanol, ethanol, acetic acid, chloroform, methylene chloride, carbon tetrachloride, dioxane, acetonitrile, tetrahydrofuran or dimethylformamide.

There is no limitation to the present reaction temperature, and the reaction is usually conducted under cooling, at ambient temperature or at somewhat elevated temperature.

(11) Process 11: (XVII)→(XVIII)

In this process, the object compound (XVIII) can be prepared by reacting the compound (XVII) or its derivative at carboxy with an acylating agent. The derivative at carboxy of the starting compound (XVII) are the same as those illustrated in the explanation of the compound (I).

Acylating agents to be used in the present reaction may include the same example as those illustrated in the explanation of the acylating agents for Process 1.

The acylation of the present process is conducted in a conventional manner, and the reaction conditions, for example, the solvent to be used and the reaction temperature are substantially the same as those explained in the acylation for Process 1.

(12) Process 12: (XIX)→(XX)

In this process, the object compound (XX) can be prepared by oxidizing the compound (XIX) or its derivative at carboxy.

The derivative at carboxy of the starting compound (XIX) are the same as those illustrated in the explanation for the compound (I).

Oxidation in the present reaction is conducted in a conventional manner with a conventional oxidizing agent which can oxidize a —S— group into

$$\overset{O}{\uparrow}\atop{—S—}$$

group.

Suitable examples of the oxidizing agent are inorganic peracid or its salt (e.g., periodic acid persulfuric acid, or the sodium or potassium salt thereof); an organic peracid or its salt (e.g., perbenzoic acid, m-chloroperbenzoic acid, performic acid, peracetic acid, chloroperacetic acid, trifluoroperacetic acid, or the sodium or potassium salt thereof); ozone, hydrogen peroxide or urea-hydrogen peroxide.

The present reaction is preferably conducted in the presence of a compound comprising a Group Vb or VIb metal in the Periodic Table, for example, tungstic acid, molybdic acid, vanadic acid, or their salt with an alkali metal (e.g., sodium, potassium), an alkaline earth metal (e.g., calcium, magnecium) or ammonium, or vanadium pentoxide.

The present oxidation is usually conducted in a solvent such as water, acetic

acid, chloroform, methylene chloride, alcohol (e.g., methanol, ethanol), tetrahydrofuran, dioxane, dimethylformamide or any other solvent which does not give bad influence to the present reaction.

There is no particular limitation to the reaction temperature, and the present reaction is usually conducted at ambient temperature or under cooling.

(13) Process 13: (XXI)→(XXII)

In this process, the object compound (XXII) can be prepared by reacting the compound (XXI) or its derivative at carboxy with an aryl halide of the formula; R'—X', wherein R' is aryl substituted by at least one substituent nitro and esterified carboxy and X' is halogen.

The derivative at carboxy of the starting compound (XXI) is the same as those illustrated in the explanation for the compound (I).

Suitable examples of aryl in the aryl substituted by at least one substituent of nitro and esterified carboxy for R' are the same as illustrated in the explanation of the definitions of R_{21} and R_{22} for the compound (XXII), and suitable examples of halogen are chlorine, bromine. Further, examples of the ester in the esterified carboxy may include the same as those illustrated in the explanation of the ester for the definition of A for the compound (I).

The present reaction is usually conducted in a solvent such as water, methanol, ethanol, propanol, tetrahydrofuran, dioxane, acetone, N,N-dimethylformamide, methylenechloride, chloroform, carbon tetrachloride or any other solvent which does not give bad influence to the present reaction.

The present reaction is preferably conducted in a base such as an inorganic or an organic base, for example, alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide), an alkaline earth metal hydroxide (e.g., magnesium hydroxide, calcium hydroxide), an alkali metal carbonate (e.g., sodium carbonate), an alkaline earth metal carbonate (e.g., calcium carbonate), an alkali metal alkoxide (e.g., sodium alkoxide, potassium alkoxide), an alkaline metal alkoxide (e.g., calcium alkoxide, barium alkoxide), an organic amine (e.g., trimethylamine), a basic ionexchange resin.

There is no particular limitation to the reaction temperature, and the present reaction is usually conducted under cooling, at ambient temperature or at an elevated temperature.

(14) Process 14: (XXIII)→(XXIV)

In this process, the object compound (XXIV) can be prepared by reacting the compound (XXIII) or its derivative at carboxy with a carbonyl compound of the formula: $R''''\!-\!\overset{R'''}{C}\!=\!O$ wherein R''' and R'''' are same or different hydrogen or alkyl, or its acetal or ketal, and then reducing the resulting product.

The derivative at carboxy of the starting compound (XXIII) are the same as those illustrated in the explanation of the derivative of carboxy for " A " with respect to the compound (I).

Examples of alkyl in a carbonyl compound are methyl, ethyl propyl, butyl, isobutyl, pentyl which may be substituted by at least one substituent of carboxy, alkoxy carbonyl, and halogen (chlorine, bromine), and examples of aralkyl are benzyl, phenethyl, phenylpropyl, naphthylmethyl, whose aryl moiety may be substituted at least one substituent of the above substituent. Suitable examples of the carbonyl compound may include an aldehyde such as alkane aldehyde (e.g., formaldehyde, acetaldehyde, propionaldehyde, butylaldehyde, isobutylaldehyde, valeraldehyde) and aralkane aldehyde (e.g., benzaldehyde), and a ketone (e.g., acetone, methylethylketone, diethylketone, methylpropylketone, methylphenylketone, methyltolylketone).

The resulting product which is produced by reacting the compound (XXIII) or its derivative at carboxy with the carbonyl compound can be subjected to the following reduction with isolation or without isolation thereof.

In the following reaction, the reduction is conducted in a conventional manner including the substantially same methods and reaction condition (solvent, temperature) as illustrated in the explanation of the reduction for Process 6.

The first step of this reaction is usually conducted in an inert solvent which does not give bad influence to the reaction such as water, dioxane, methanol, ethanol or N,N-dimethylformamide. The carbonyl compound in liquid may be also used as a solvent.

There is no particular limitation to the reaction temperature, which is selected depending on a kind of the carbonyl compound to be used and the reducing agent to

be used, and the reaction is usually conducted under cooling or at ambient or somewhat elevated temperature.

In this reaction, in the course of the reaction or post-treatment, the derivative at carboxy may be converted into the corresponding carboxy,

$$\begin{array}{c} -C- \\ \| \\ NOH \end{array}$$

may be converted into

$$\begin{array}{c} -CH- \\ | \\ NH_2 \end{array}$$

by reduction, and the substituent, halogen may be converted into hydrogen by dehalogenation. The cases as above are included within the scope of the present invention.

(15) Process 15: (XXV)→(XXVI)

In this process, the compound (XXVI) can be prepared by reducing the compound (XXV) or its derivative at carboxy,

Examples of the derivative at carboxy of the starting compound (XXV) are the same as those illustrated in the explanation for the compound (I).

In this reaction, the reduction is conducted in a conventional manner, and examples of the reducing agents and the reduction conditions are substantially the same as illustrated in the explanation of the reduction for Process 6.

(16) Process 16: (XXVII)→(XXVIII)

In this process, the compound (XXVIII) can be prepared by reacting the compound (XXVII) or its derivative at carboxy with an amine compound of the formula; R_{27}—NH_2 wherein R_{27} is as defined above.

Examples of the derivative at carboxy of the starting compound (XXVII) may include same ones as illustrated in the explanation for the compound (I).

Examples of alkoxy group and alkanoyl moiety in the alkanoylamino in the definitions for R_{27} in the amine compound are the same as illustrated in the above explanation for the compound (XXVII).

In the reaction, the amine compound (R_{27}—NH_2) may be used in the form of its salt with an acid such as inorganic salt (e.g. hydrochloric acid, sulfuric acid) and organic acid (e.g. formic acid, acetic acid), and in this case the reaction may be preferably conducted under alkaline condition, for example, in the presence of alkali metal (e.g., sodium hydroxide, potassium hydroxide) or alkaline earth metal (e.g., calcium hydroxide).

The reaction is usually conducted in an inert solvent. Suitable examples of the solvent are water and an hydrophilic solvent such as methanol, ethanol, propanol, and N,N-dimethyl formamide, and any other solvent which does not give bad influence to the present reaction.

There is no particular limitation to the reaction temperature, and the present reaction is usually conducted under cooling at ambient temperature or at somewhat elevated temperature.

(17) Process 17: (XXIX)→(XXX)

In this process, the object compound (XXX) can be prepared by acylating the compound (XXIX) or its derivative at carboxy with an acylating agent.

Examples of the derivative at carboxy of the starting compound are the same as those illustrated in the explanation for the compound (I).

Examples of acylating agent and acyl group in acylamino for R_{2}, may include the examples as illustrated in the explanation for Process 1.

The acylation reaction of the present conditions, for example, the solvent and the reaction temperature, are also the same.

This process is conducted in a conventional manner, and may be conducted in substantially the same conditions (e.g., solvent, reaction temperature) as those mentioned in the explanation for Process 1.

(18) Process 18: (XXXI)→(XXXII)

In this process, the object compound (XXXII) can be prepared by reacting the compound (XXXI) or its derivative at carboxy with a hydroxyalkane sulfonic acid of the formula;

$$HO-\underset{R_{32}\ \ R_{33}}{C}-SO_3H$$

or the salt thereof, wherein R_{32} and R_{33} are as defined above.

Examples of the derivative at carboxy of the starting compound (XXXI) are the same as those illustrated in the explanation for the compound (I).

Examples of alkyl in the definitions of R_{32} and R_{33} for the above reagent, hydroxyalkane sulfonic acid, are illustrated in the explanation for the compound (XXXII). As an example of the salts of said hydroxyalkane sulfonic acid, there may be illustrated an salt with metal such as alkali metal (e.g. sodium, potassium) or alkaline earth metal (e.g. calcium, magnesium).

The hydroxyalkanesulfonic acid to be used as a reagent can be prepared by reacting a carbonyl compound of the formula

$$R_{32}-\underset{\underset{O}{\|}}{C}-R_{33}$$

(wherein R_{32} and R_{33} are as defined above) with sulfurous acid or the salt thereof (e.g. alkali or alkaline earth metal). Then, the object compound (XXXII) may be also prepared by reacting the compound (XXXI) with the above carbonyl compound and thereafter with the sulfurous acid or the salt thereof, the case of which is included within the scope of the present process.

The reaction is usually conducted in a solvent. As examples of the suitable solvents, there may be illustrated water hydrophilic solvent such as methanol, ethanol, propanol, tetrahydrofuran, dioxane, N,N-dimethylformamide, and the mixture thereof, and any other solvent which does not give bad influence to the present reaction.

There is no particular limitation to the reaction temperature, and the present reaction is usually conducted under cooling, at ambient temperature or at an elevated temperature.

In the course of the reaction, amino group of the compound (XXXI) may react with the hydroxyalkanesulfonic acid to be converted into the corresponding di-substituted amino group

$$[-N(-\underset{R_{32}\ \ R_{33}}{C}-SO_3H)_2 \text{ or the salt thereof}],$$

the case of which is also included within the scope of the present process.

When the hydroxyalkanesulfonic acid is used as a reagent the reaction is preferably conducted in the presence of alkali or alkaline earth metal.

(19) Process 19: (XXXIII)→(XXXIV)

In this process, the compound (XXXIV) having esterified carboxy group ($-COOR_{39}$ and $-COOR_{41}$ wherein R_{39} and R_{41} are a group which is derived from an esterifying agent) can be prepared by reacting the compound (XXXIII) with a conventional esterifying agent.

Examples of esterified carboxy of the object compound may include the same as illustrated in the explanation of the ester for the derivative of carboxy for the compound (I) including silyl ester, aliphatic ester, ester containing aromatic or heterocyclic ring.

Esterifying agent may include any conventional agent which can esterify a carboxy group to provide an esterified carboxy group.

Suitable esterifying agents may include a halide compound such as alkyl halide (e.g., methyliodide, ethylbromide, ethyliodide, propylbromide; substituted alkylhalide such as alkanoyloxy alkylhalide (e.g., acetoxymethylchloride, acetoxyethylchloride acetoxypropylbromide), aroylalkylhalide (e.g., phenacyl bromide) or an aralkylhalide (e.g., benzylchloride, phenethylchloride);

a dialkyl sulfate (e.g., dimethyl sulfate, diethyl sulfate, dipropyl sulfate);

an alkyl sulfonate (e.g., methyl benzenesulfonate, methyl p-toluenesulfonate, ethyl 4-bromobenzenesulfonate);

a holoformate such as alkyl haloformate (e.g., methyl chloroformate, ethyl chloroformate, propyl chloroformate;

a diazoalkane (e.g., diazomethane, diazoethane) and;

a hydroxy compound such as alcohol, for example, an alkanol (e.g., methanol,

ethanol, propanol, 2-chloroethanol, 2,2,2-trichloroethanol, butanol, 1-cyclopropyl-ethanol); and an aralkanol (e.g., benzylalcohol, diphenylmethanol, phenethylalcohol).

In case that the hydroxy compound is used as a esterifying agent in this process, the reaction may be preferably conducted in the presence of a condensing agent such as those illustration in the explanation of the condensing agent for process 1.

In the course of the present reaction, hydrogen atom in the hydroxy group of the starting compound (XXXIII) may be replaced by a group which is derived from an esterifying agent, that is the said hydroxy group may be, for example, alkylated, aralkylated. Such cases as mentioned above are included within the scope of the present process.

The reaction is usually conducted in a solvent such as water, dioxane, acetone, pyridene, N-N-dimethylformamide or ether.

There is no particular limitation to the reaction temperature, and the reaction is usually conducted under cooling at ambient temperature or an elevated temperature.

(20) Process 20: (XXXV)→(XXXVI)

In this process, the object compound (XXXVI) can be prepared by oxidizing the compound (XXXV) or its derivative at carboxy. Examples of the derivative at carboxy of the starting compound (XXXV) are the same as those illustrated in the explanation for the compound (I).

The present oxidation are conducted in a conventional manner.

As examples of the oxidizing agents, there may be employed such examples as illustrated for the oxidizing agents for Process 12.

The reaction of the present process also are conducted under substantially same conditions (e.g. solvent, reaction temperature) as mentioned in the explanation of Process 12.

(21) Process 21: (XXXVII)→(XXXVIII)

In this process, the object compound (XXXVIII) can be prepared by reacting the compound (XXXVII) or its derivative at carboxy with a diazotizating agent and then solvolyzing the resulting diazonium salt.

The examples of derivative at carboxy of the starting compound (XXXVII) are the same as those illustrated in the explanation of the derivative of carboxy for "A" with respect to the compound (I).

Suitable examples of diazotizing agent to be used in the reaction may include dinitrogen trioxide; nitrous acid or its derivative such as alkyl ester (e.g., methyl nitrite, ethyl nitrite, amyl nitrite), alkali metal salt (e.g., sodium nitrite, potassium nitrite); and mixed anhydride (e.g., nitrosyl chloride, nitrosyl bromide, nitrosylsulfuric acid, nitrosylacetic acid).

The diazotization is usually conducted in a solvent such as water, methanol, ethanol, N,N-dimethylformamide, dimethylsulfoxide or any other solvent which does not give bad influence to the reaction.

The resulting diazonium salt which is produced by reacting the compound (XXXVII) or its derivative at carboxy with a diazotizating agent is solvolyzed by treating the reaction mixture *per se* or the isolated diazonium salt under acidic condition in the presence of an acid such as an inorganic acid (e.g., hydrochloric acid, sulfuric acid, phosphoric acid, nitric acid) and an organic acid (e.g., formic acid, acetic acid, propionic acid, butyric acid, p-toluenesulfonic acid).

There is no limitation to the present reaction temperature and the reaction is usually carried out under cooling, at ambient temperature, or at an elevated temperature.

In the present reaction, the amino group in the starting compound (XXXVII) is first diazotizated and then the resulting diazonium salt is solvolyzed to the corresponding hydroxy group. Then, depending upon a kind of the diazotizing agent to be used, the object compound (XXXVIII) or its derivative at carboxy can be prepared by one step by diazotizing the compound (XXXVII) or its derivative at carboxy, under acidic condition, i.e. in an acidic solvent selected from a liquid inorganic or organic acid as stated above and a mixture of the inorganic or organic acid and the solvent as mentioned above, whereby the object compound (XXXVIII) are obtained without any specific solvolysis treatment.

(22) Process 22: (XXXIX)→(XXXX)

In this process, the object compound (XXX) can be prepared by reacting the compound (XXXIX) or its derivative at carboxy with an aryl halide of the formula: R″X′ wherein R″ is aryl which may be substituted by at least one substituent of nitro, esterified carboxy and aromatic heterocyclic group, and X′ is halogen.

Examples of the derivative at carboxy of the starting compound (XXXIX) are the same as those illustrated in the explanation for the compound (I).

Suitable examples of aryl in the aryl which may be substituted by at least one substituent of nitro, esterified carboxy and aromatic heterocyclic group for R_{43} are the same as those illustrated in the explanation for Process 13 (to be referred to the explanation of the compound (XXII)).

Further, examples of the ester in the esterified carboxy may include the same as those illustrated in the explanation of the ester for the definition of A for the compound (I). Examples of the aromatic heterocyclic group are illustrated in the explanation for the compound (XXXIX).

The reaction is conducted under substantially the same conditions (solvent, reaction temperature) as those explained in the explanation of the reaction for the Process 13.

(23) Process 23: (XXXXI)→(XXXXII)

In this reaction, the object compound (XXXXII) can be prepared by reacting the compound (XXXXI) with an alkylating agent.

Suitable alkylating agents may include, for example, alkanol (e.g., methanol, ethanol, propanol, isopropyl alcohol, butanol), diazoalkane (e.g., diazomethane, diazoethane), dialkyl sulfate (e.g., dimethyl sulfate, diethyl sulfate, dipropyl sulfate), alkyl tosylate (e.g., methyl tosylate, ethyl tosylate).

The present reaction is usually conducted in a solvent such as methanol, ethanol, acetone, ether, dimethylformamide and any other solvent which does not give bad influence to the reaction.

In case that diazoalkane, dialkyl sulfate or alkyl tosylate is used as an alkylating agent in the present reaction, both of carboxy and hydroxy groups of the compound (XXXXI) are usually alkylated, but in case that alkanol is used as an alkylating agent, carboxy group of the compound (XXXXI) is selectively alkylated.

When dialkyl sulfate, alkyl tosylate is employed as an alkylating agent in the present reaction, the reaction may be preferably conducted in the presence of a base such as an inorganic base (e.g., sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate) and an organic base (e.g., trimethylamine, triethylamine, pyridine, picoline), and when alkanol is employed as an alkylating agent in the present reaction, the reaction is preferably conducted in the presence of a conventional condensing agent such as 1-(4-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole.

There is no particular limitation to the present reaction temperature, and it may be suitably selected in accordance with kinds of the compound (XXXXI) and, an alkylating agent to be used. For example, when diazoalkane is employed in the present reaction, the reaction may proceed under cooling or at ambient temperature.

(24) Process 24: (XXXXIII)→(XXXXIV)

In this process, the object compound (XXXXIV) can be prepared by subjecting the compound (XXXXIII) to elimination reaction of the protective group of amino.

The present elimination reaction is conducted in a conventional manner, that is under substantially the similar conditions as those described in the elimination reaction of the protected group of amino of the compound (XIII) in Process 9.

Examples of the protected group may include the same as those illustrated in the explanation with respect to the compound (IV).

In this reaction, in case that the starting compound (XXXXIII) has the other protected amino, protected hydroxy and/or protected carboxy group, such protected group may be eliminated in the reaction to be converted into the corresponding amino, hydroxy and/or carboxy group, whose reaction is also included within the scope of the present process.

(25) Process 25: (XXXXV)→(XXXXVI)

In this process, the object compound (XXXXVI) can be prepared by reacting the compound (XXXXV) with a reagent selected from hydrazide, hydroxyalkylamine and aralkylamine or the salt thereof.

Suitable examples of hydroxyalkylamine may include hydroxyethylamine and hydroxypropylamine, and suitable examples of aralkylamine may include benzylamine and phenethylamine.

Suitable examples of the salts of hydrazide, hydroxyalkylamine or aralkylamine may include an organic acid salt (e.g., acetate, maleate, tartrate, benzenesulfonate, toluenesulfonate) and an inorganic acid salt (e.g., hydrochloride, sulfate, phosphate).

The present reaction can be conducted under substantially the similar conditions as those described in the explanation of the acylation of the compound (II) in Process 1.

(26) Process 26: (XXXXVII)→(XXXXVIII)

In this process, the object compound (XXXXVIII) can be prepared by reacting the compound (XXXXVII) with an esterified alkene carboxylic acid.

Examples of alkene moiety in the esterified alkene carboxylic acid may include alkenyl which may be branched, such as 1-propenyl, 1-butenyl, 1-pentenyl, isopropenyl, methylpropenyl, methylbutenyl, methylpentenyl, ethylpropenyl, ethylbutenyl, and examples of ester moiety therein may include a non-reactive ester in the ester as illustrated in the explanation of the ester with respect to the compound (I), (I') and (II).

The present reaction is usually conducted in a solvent which does not give bad influence to the reaction such as water, methanol, ethanol, acetone, chloroform or dimethylformamide.

The present reaction can be preferably conducted in the presence of a base such as an inorganic base (e.g., sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate) and an organic base (e.g., trimethylamine, triethylamine, pyridine, picoline).

There is no particular limitation to the present reaction temperature, and the reaction may proceed under cooling or warming.

(27) Process 27: (XXXXVII)→(XXXXIX)

The object compound (XXXXIX) can be prepared by reacting the compound (XXXXVII) or its salt with an esterified aliphatic hydrocarbon carbonyl acetic acid or its salt.

Examples of aliphatic hydrocarbon moiety in the esterified aliphatic hydrocarbon carbonyl acetic acid may include the same as those illustrated in the explanation of that in the acyl for the compound (I). Suitable example of the esterified aliphatic hydrocarbon carbonyl acetic acid is esterified alkanoylacetic acid such as esterified acetyl, propinoyl, butyryl acetic acid. Examples of ester moiety in esterified aliphatic hydrocarbon carbonyl acetic acid may include a non-reactive ester in the ester as illustrated in the explanation of the ester with respect to the compound (I), (I') and (II).

Suitable salt of the compound (XXXXVII) may include an organic acid salt (e.g., acetate, maleate, tartrate, benzenesulfonate, toluenesulfonate) and an inorganic acid salt (e.g., hydrochloride, sulfate, phosphate), and a suitable salt of an alkanoylacetic acid ester may include an inorganic base salt (e.g., sodium salt, potassium salt, calcium salt, magnesium salt).

The present reaction can be conducted with or without solvent. Suitable solvents may include methanol, ethanol, propanol, ether, acetone, benzene, toluene and any other solvent which does not give bad influence to the reaction. The present reaction can be preferably conducted in the presence of a base such as an inorganic base (e.g., sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate) and an organic base (e.g., trimethylamine, triethylamine, pyridine, picoline).

There is no particular limitation to the present reaction temperature, and the present reaction are usually conducted under warming or heating.

Thus obtained object compound (XXXXIX) may include an isomer of the compound (XXXXIX) wherein R_{53} is replaced by an acylamino having alkylidenamino substituted by esterified carboxy.

(28) Process 28: (XXXXXII)→(XXXXVII)

In this process, the object compound (XXXXVII) can be prepared by reducing the compound (XXXXXII).

The reduction is conducted in a conventional manner in which nitro and azido group can be reduced to amino group, including the reduction method as described in the reduction for Process 15.

Suitable reduction applicable for the reaction may include a chemical reduction using a metal (e.g., tin, zinc, iron) and an acid (e.g., acetic acid, hydrochloric acid) or a catalytic reduction in the presence of a metallic catalyst such as palladium carbon, Raney-nickel, platinum oxide and other conventional catalysts.

The reaction is conducted in a solvent such as methanol, ethanol or propanol.

There is no particular limitation to the present reaction temperature, and it may suitably selected in accordance with kinds of the compound (XXXXXII) and reduction methods.

(29)-(a) Process (29-(a): (XXXXXIII)→(XXXXXIV)

In this process, the object compound (XXXXXIV) can be prepared by reducing the compound (XXXXXIII).

The reduction is conducted in a conventional manner. Suitable reduction applicable for the present reaction may be, for example, reduction using an alkali metal borohydride (e.g., sodium borohydride, lithium borohydride).

The present reaction is usually conducted in a solvent which does not give bad influence to the reaction such as water, methanol, ethanol, chloroform, benzene or toluene.

There is no particular limitation to the present reaction temperature, and it may be suitably selected in accordance with kinds of the compound (XXXXXIII) and reduction methods.

(29)-(b) Process 29-(b): (XXXXXV)→(XXXXXVI)

In this process, the object compound (XXXXXVI) can be prepared by reacting the compound (XXXXXV) or its derivative at carboxy with an aralkylamine under reductive condition.

Suitable examples of aralkylamine are benzylamine and phenethylamine, whose benzene ring may be substituted by at least one suitable substituent.

Examples of the derivative at carboxy of the starting compound (XXXXXV) are the same as illustrated in the explanation of the derivative of carboxy for " A " with respect to the compound (I).

The present reaction is conducted under reductive conditions, that is by reacting the starting compound (XXXXXV) with an aralkylamine in the presence of a conventional reducing agent or by reacting the starting compound (XXXXXV) with an aralkylamine and then reducing the resulting product with a conventional reducing agent.

Suitable examples of the reducing agents are, an alkali metal borohydride (e.g., sodium borohydride, potassium borohydride), and other conventional reducing agent and methods as illustrated in Process 6 can be used.

In case that the reaction is conducted by reacting the compound (XXXXXV) with an aralkylamine and then reducing the resulting product, the reaction of the compound (XXXXXV) with an aralkylamine can be preferably conducted in the presence of base such as an inorganic base (e.g., sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate) and an organic base (e.g., trimethylamine, triethylamine, pyridine, picoline).

The present reaction is usually carried out in a solvent which does not give bad influence to the reaction such as methanol, ethanol, chloroform, benzene or toluene.

There is no particular limitation to the present reaction temperature, and it may be suitably selected in accordance with kinds of the compound (XXXXXV), aralkylamine and reduction conditions or reduction methods.

(30) Process 30: (XXXXXVII)→(XXXXXVIII)

In this process, the object compound (XXXXXVIII) can be prepared by reacting the compound (XXXXXVII) or its derivative at carboxy with a trialkylamine.

Examples of the derivative at carboxy are the same as illustrated in the explanation of the derivative of carboxy for " A " with respect to the Compound (I).

Suitable trialkylamines may include trimethylamine, triethylamine and tripropylamine.

The present reaction is usually conducted in a solvent which does not give bad influence to the reaction such as methanol, ethanol, acetone, ether, dimethylformamide and the like.

There is no particular limitation to the present reaction temperature, and the reaction is usually conducted at ambient temperature or under warming.

(31) Process 31: (XXXXX)→(XXXXXI)

In this process, the object compound (XXXXXI) can be prepared by reacting the compound (XXXXX) or its derivative at carboxy with an aralkanoylating agent.

The derivative at carboxy of the starting compound (XXXXX) are the same as illustrated in the explanation of the derivative of carboxy for " A " with respect to the compound (I).

The aralkanoylation is conducted in a conventional manner, and the reaction is conducted under substantially the same condition (solvent, reaction temperature) as illustrated in the acylation for Process 1.

Examples of aralkanoylating agents may include the same as illustration in the explanation of the acylating agent for Process 1.

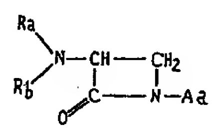
According to kinds of the reactions to be used in the afore-mentioned Processes, the carboxy group may be converted into the corresponding derivative at carboxy and/or the derivative at carboxy may be converted into the corresponding free carboxy group in the course of the reaction of the starting compounds or the post treatment of the reaction mixtures or the object compounds. In the same manner, protected group(s) of the protected carboxy, protected amino and/or protected hydroxy, may be converted into the corresponding carboxy, amino and/or hydroxy group(s), respectively. Such cases of the reactions as mentioned above also include within the scope of the Processes as concerned in the present invention.

The object compounds (I) of the present invention have antimicrobial activities against various pathogenic microorganisms and may be useful for treatment of diseases infected by such microorganisms in human being and animals.

With regard to the representative object compounds of the present invention, their antimicrobial activities against pathogenic microorganisms are illustrated as M.I.C. (Minimum Inhibitory Concentration) value determined in a conventional manner as followed. In the following, M.I.C. value is shown as microgram per ml.

An object compound of Example 39, *Pseudomonas aeruginosa* (3); an object compound of Example 51, *Bacillus subtilis* (12.5); an object compound of Example 112, *Escherichia coli* (60), *Proteus vulgaris* (<3), *Staphylococcus aureus* (60); an object compound of Example 157, *Bacillus subtilis* (7.5), *Staphylococcus aureus* (7.5); an object compound of Example 158, *Bacillus subtilis* (80), *Staphylococcus aureus* (80); an object compound of Example 161, *Escherichia coli* (16), *Proteus vulgaris* (8), *Staphylococcus aureus* (8); an object compound of Example 291, *Escherichia coli* (1.6), *Proteus vulgaris* (25); an object compound of Example 300, *Pseudomonas aeruginosa* (15), *Escherichia coli* (60); an object compound of Example 400, *Pseudomonas aeruginosa* (32), *Escherichia coli* (16); an object compound of Example 469, *Bacillus subtilis* (60), *Escherichia coli* (4), *Staphylococcus aureus* (4); an object compound of Example 489, *Pseudomonas aeruginosa* (15), *Escherichia coli* (3.9), *Proteus vulgaris* (60); an object compound of Example 507, *Pseudomonas aeruginosa* (6.3), *Proteus vulgaris* (25); an object compound of Example 508, *Pseudomonas aeruginosa* (6.3), *Proteus vulgaris* (25); an object compound of Example 511, *Bacillus subtilis* (6), *Escherichia coli* (30), *Staphylococcus aureus* (60).

As previously mentioned, most of the compounds produced by the processes according to the invention are new. The new compounds may be particularly represented by the following formula.



in which

(1) R_a and R_b are each hydrogen,

(2) R_a is hydrogen and R_b is hydrocarbon sulfonyl (such as arene sulfonyl),

(3) R_a and R_b together form a bivalent acyl group derived from a dicarboxylic acid (e.g. phthalic acid),

(4) R_a is hydrogen and

R_b is

4-aminobenzoyl,

3,5-diaminobenzoyl,

2-[4-(2-chloroacetyl)phenyl]acetyl,

3-phenylacryloyl,

4-(2-phenoxyacetamido)benzoyl,

3-(2-chlorophenyl)-5-methyl-4-isoxazolecarbonyl,

2,2-dimethylpropionyl,

3-(3-oxo-1,2-oxazolidin-4-yl)carbamoyl,

3-methylthioacryloyl,

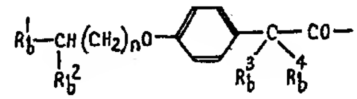
2 - [2 - [4 - chloro - 2 - {4 - (2 - bromoacetamido)benzoyl} - phenoxy]acetamido] - 2 - phenylacetyl,

2 - [2 - benzyloxyimino - 2 - (4 - methoxyphenyl)acetamido] - 2 - phenylacetyl,

2 - [4 - (4 - chloroanilinomethyl)phenoxy] - 2 - methylpropionyl,

2 - [2 - [4 - chloro - 2 - [4 - {2 - (2 - pyridylthio)acetamido} - benzoyl]phenoxy]acetamido] - 2 - phenylacetyl, or an acyl group as mentioned in the explanation of

an acyl group for R_1, and more particularly an acyl group selected from the following groups:—

(i) 

wherein

n is an integer 0—4

R_b^1 is hydrogen; or carboxy or its derivative (e.g., the salt, the ester),

R_b^2 is hydroxy; halogen; azido; amino; aliphatic radical-amino such as alkylamino, alkenylamino, cycloalkylamino, arylamino; acylamino such as aliphatic acylamino (e.g., alkanoylamino), aliphatic radical-oxy(thiocarbonyl)amino [e.g., alkoxy(thiocarbonyl)amino], aryloxy-aliphatic acylamino (e.g., aryloxyalkanoylamino), aryl-aliphatic acylamino (e.g., aralkanoylamino), heterocyclic-aliphatic acylamino (e.g., heterocyclic alkanoylamino), aroylamino; substituted ureido such as N′-arylureido; substituted thioureido such as N′-arylthioureido; or arylthio.

R_b^3 is hydrogen; hydroxy; amino; arylamino; acylamino such as aliphatic acylamino (e.g., alkanoylamino), aliphatic radical-oxy(thiocarbonyl)amino [e.g., alkoxy-(thiocarbonyl)amino], aroylamino; substituted ureido such as N′-arylureido; or substituted thioureido such as N′-arylthioureido,

R_b^4 is hydrogen, or

R_b^3 and R_b^4 together form oxo; hydroxyimino; or substituted hydroxyimino such as alkoxyimino,

in which the aliphatic hydrocarbon moiety may be substituted by at least one suitable substituent of carboxy or its derivative (e.g., the salt, the ester), halogen, sulfo, and the aryl and heterocyclic ring may be substituted by at least one suitable substituent of nitro, halogen carboxy or its derivative (e.g., the salt, the ester).

(ii) $R_b^6—\underset{\underset{R_b^5}{\|}}{C}—CO—$:

in which

R_b^5 is oxo; hydroxyimino; or substituted hydroxyimino such as aliphatic radical-oxyimino (e.g., alkoxyimino), aryl-aliphatic radical-oxyimino (e.g., aralkoxyimino).

R_b^6 is cyano; aliphatic radical such as alkyl; aryl; heterocyclic radical; aliphatic radical-amino such as alkylamino; aryl-aliphatic radical-amino such as aralkylamino; or aliphatic radical-oxy such as alkoxy,

in which the aliphatic moiety may be substituted by at least one suitable substituent such as hydroxy, carboxy or its derivative (e.g., the salt, the ester) and the aryl and heterocyclic ring may be substituted by at least one suitable substituent such as hydroxy, aliphatic radical-oxy (e.g., alkoxy, alkenyloxy) which may have carboxy or its derivative, aryl-aliphatic radical-oxy (e.g., aralkoxy).

(iii) $R_b^7—CO—$:

wherein

R_b^7 is aryl; aryloxy; aryl-aliphatic radical-oxy such as aralkyloxy; arylamino; heterocyclic radical; guanidino; or substituted guanidino such as acylguanidino (e.g., 3-aralkanoylguanidino),

in which aryl and heterocyclic radical may be substituted at least one suitable substituent such as nitro, halogen, aliphatic radical (e.g., alkyl), aliphatic radical-oxy (e.g., alkoxy)

(iv) $R_b^9—(CH_2)_{n_2}—\underset{\underset{R_b^8}{|}}{CH}—(CH_2)_{n_3}—CO—$:

wherein

n_2 and n_3 are each 0 or an integer of 1—4,

R_b^8 is hydrogen; aliphatic radical such as alkyl; aryl; substituted oxy such as aryloxy; heterocyclic radical; or N-substituted carbamoyl such as N-arylcarbamoyl,

in which the aryl and heterocyclic radical may be substituted by at least one suitable substituent (e.g., hydroxy).

R_b^a is hydrogen; amino; azido; halogen; hydroxy; carboxy or its derivative (e.g., the salt, the ester); sulfo; substituted sulfo such as arylsulfo; aliphatic radical such as alkyl, alkenyl,
which may be substituted by at least one suitable substituent selected from amino, protected amino, azido, halogen, hydroxy, carboxy or its derivative (e.g., the salt, the ester), sulfo, acyl (e.g., aroyl), N,N-disubstituted amino (e.g., N-alkyl-N-arylamino alkyl), aryl, substituted aryl, heterocyclic radical and substituted heterocyclic radical;

aryl
which may be substituted by at least one suitable substituent selected from hydroxy, nitro, carboxy, halogen and substituted sulfonamido [e.g., aromatic ring sulfonamido (e.g., benzenesulfonamide) which may have at least one substituent (e.g., carboxy, hydroxy)];

heterocyclic radical
which may be substituted by at least one suitable substituent selected from aliphatic radical, aryl, heterocyclic radical and acylamino [e.g., heterocyclic radical, alkyl-heterocyclic radical, aryl-heterocyclic radical, heterocyclic-heterocyclic radical, heterocyclic-aliphatic acyl (e.g. heterocyclicalkanoyl) amino-heterocyclic radical, arylaliphatic acyl (e.g. aralkanoyl) amino-heterocyclic radical in which aryl and heterocyclic ring may have at least one suitable substituent (e.g. oxo, halogen)];

acyl such as
aroyl;

aliphatic radical-oxy such as
alkoxy, cycloalkyloxy which may be substituted by at least one suitable substituent;

aryloxy
whose aryl ring may be substituent by at least one substituent selected from nitro, halogen, acyl (e.g., formyl, alkanoyl), acylamino (e.g., alkanoylamino), aryl, aryl-aliphatic radical amino (e.g., aralkylamino), and aliphatic radical (e.g., alkyl, alkenyl) which may be substituted by at least one suitable substituent [e.g., carboxy or its derivative (the salt, the ester), amino, hydroxy, nitro, hydroxyimino, substituted hydroxyimino such as aliphatic radical-oxyimino (e.g., alkoxyimino), which may be substituted by carboxy, (N-halo-N,N,N-trialiphatic radicalammonio)aliphatic acyl-hydrazono (e.g., (N-halo-N,N,N-trialkylammonio)-alkanoylhydrazono), aliphatic radical-thio-aliphatic acylamino (e.g., alkylthioalkanoylamino) in which aliphatic-thio moiety may be substituted by at least one suitable substituent (e.g., amino, carboxy)];

heterocyclic-oxy;

aliphatic radical-thio
which may be substituted by at least one suitable substituent selected from amino, carboxy, acyl and acylamino, [e.g., alkylthio, alkenylthio, acylamino-aliphatic radical thio (e.g., aroylalkanoylamino-alkylthio) acyl-aliphatic radical-thio (e.g., aroyl-alkylthio, N-arylcarbamoyl-alkylthio) which may have at least one suitable substituent (e.g., halogen, nitro)];

aliphatic radical-sulfinyl
which may be substituted by at least one suitable substituent selected from substituted carbamoyl, (e.g., alkylsulfinyl, N-arylcarbamoylalkylsulfinyl);

arylthio
which may be substituted by carboxy;

heterocyclic-thio
which may be substituted by at least one suitable substituent of amino, hydroxy, amino aliphatic radical or acylamino-aliphatic radical, [e.g., heterocyclic-thio, aminoalkyl-heterocyclic-thio, alkanoylaminoalkyl-heterocyclic thio), which may have at least one suitable substituent (e.g., hydroxy);

arylamino
which may be substituted by at least one suitable substituent;

heterocyclic-amino
which may be substituted by at least one suitable substituent selected from oxo, aryl (e.g., oxo-substituted heterocyclic amino, aryl-heterocyclic amino);

mono- or di- substituted amino such as
aliphatic radical-amino (e.g., alkylamino), N-aliphatic radical -N-protected- amino (e.g., N-alkyl-N-protected carboxy amino), N-substituted-N-arylamino [e.g., N-aliphatic radical-N-arylamino (e.g., N-alkyl-N-arylamino)], N-acyl-N-arylamino (e.g., N-alkanoyl-N-arylamino), N-aliphatic radical-N-arylamino (e.g., N-alkyl-N-arylamino) in which aliphatic hydrocarbon moiety may have at least one suitable substituent (e.g., azido, carboxy) N-substituted sulfonyl-N-arylamino (e.g., N-alkanesulfonyl-N-arylamino];

acylamino selected from:—

aliphatic acylamino
(e.g., alkanoylamino) which may be substituted by at least one suitable substituent (e.g., halogen, amino);

aliphatic radical-oxy-aliphatic acylamino
(e.g., cycloalkyloxyalkanoyl) which may be substituted by at least one suitable substituent;

aliphatic radical-thio-aliphatic acylamino
(e.g., alkylthioalkanoylamino) in which aliphatic hydrocarbon moiety may be substituted by at least one suitable substituent (e.g., amino, halogen, carboxy);

aryl-aliphatic acylamino
in which aryl ring may be substituted by at least one suitable substituent selected from aliphatic radical oxy, aryloxy (e.g., alkoxy-aralkanoylamino, aryloxy-aralkanoylamino) in which aliphatic hydrocarbon moiety and aryl ring may have at least one suitable substituent [e.g., halogen, arylaliphatic radical-oxyimino (e.g., aralkoxyimino), arylamino, amino, hydroxy];

arylamino-aliphatic acylamino
(e.g., arylaminoalkanoylamino) in which aryl ring and aliphatic hydrocarbon moiety may be substituted by at least one suitable substituent (e.g., halogen, carboxy, amino);

aryloxy-aliphatic acylamino
whose aryl ring may be substituted by a substituent selected from aliphatic radical (e.g., alkyl), aryl, arylaliphatic radical (e.g., aralkyl), heterocyclic radical, aryl (e.g., aliphatic acyl, substituted-aroyl, heterocyclic-carbonyl) arylaliphatic radical-amino-aliphatic radical (e.g., aralkylaminoalkyl), [e.g., aryloxyalkanoylamino which may be substituted by at least one suitable substituent (e.g., halogen, nitro, caiboxy, formyl, carbazoyl);

alkyl-aryloxyalkanoylamino
which may be substituted by at least one suitable substituent (e.g., hydroxy); aryl-aryloxyalkanoylamino;

aralkyl-aryloxyalkanoylamino
which may be substituent by at least one suitable substituent (e.g., hydroxyimino, halogen);

formyl-aryloxyalkanoylamino;

alkanoyl-aryloxyalkanoylamino;

aroyl-aryloxyalkanoylamino
which may be substituted by at least one suitable substituent (e.g., nitro, amino, halogen);

alkylthioalkanoylaminoaroyl-aryloxyalkanoylamino
which may be substituted by at least one suitable substituent (e.g., halogen, amino, carboxy);

alkylthioalkylaminoaroyl-aryloxyalkanoylamino
which may be substituted by at least one suitable substituent (e.g., amino, halogen);

(N-halo-N,N,N-trialkylammonio) alkanoylaminoaroyl-aryloxyalkanoylamino
which may be substituted by at least one suitable substituent (e.g., halogen);

heterocyclic-carbonyl-aryloxyalkanoylamino
which may be substituted by at least one suitable substituent (e.g., halogen);

aralkylaminoalkyl-aryloxyalkanoylamino
which may be substituted by at least one suitable substituent (e.g., alkoxy, carboxyalkoxy, carboxy);

heterocyclic-aryloxyalkanoylamino
in which heterocyclic ring may be substituted by at least one suitable substituent (e.g., alkyl, aryl, substituted (e.g., halo) aryl) and alkane moiety may be substituted by at least one suitable substituent (e.g., halogen, amino);

diaryloxy-aliphatic acylamino
(e.g., diaryloxyalkanoylamino) in which aliphatic hydrocarbon moiety may be substituted by at least one suitable substituent (e.g., halogen, amino);

arylthio-aliphatic acyl amino
(e.g., arylthioalkanoyl amino) which may be substituted by at least one suitable substituent (e.g., carboxy);

heterocyclic-aliphatic acylamino
in which heterocyclic radical may have at least one suitable substituent [e.g., aliphatic radical (e.g., alkyl), aryl which may have a substituent (e.g., halogen)] and aliphatic hydrocarbon moiety may have at least one suitable substituent (e.g., halogen, amino);

heterocyclic-heterocyclic-aliphatic acylamino
(e.g., heterocyclic-heterocyclic-alkanoyl);

heterocyclicthio-aliphatic acyl amino
(e.g., heterocyclicthioalkanoyl amino) which may be substituted by at least one suitable substituent [e.g., hydroxy, amino, aliphatic radical (alkyl) which may have at least one suitable substituent (e.g., amino)];

acylamino-aliphatic acylamino
[e.g., arylaliphatic acylamino-aliphatic acylamino (e.g., aralkanoylamino-alkanoylamino) in which aliphatic hydrocarbon moiety and/or aryl ring may be substituted by at least one suitable substituent (e.g., amino, halogen, carboxy);

substituted sulfinyl-aliphatic acylamino
(e.g., arylsulfinylalkanoylamino) which may be substituted by at least one suitable substituent (e.g., carboxy);

substituted sulfo-aliphatic acylamino
(e.g., arylsulfoalkanoylamino);

N,N-disubstituted amino-aliphatic acylamino
(e.g., (N-aryl-N-arylsulfonylamino)alkanoylamino);

substituted glyoxyloylamino
(e.g., arylglyoxyloylamino);

substituted-oxyalylamino
(e.g., alkoxyalylamino, aralkylaminooxyalylamino);

N-substituted carbamoyl
(e.g., N-arylcarbamoyl);

guanidinocarbonylamino;

substituted sulfonamido

[e.g., aromatic ring sulfonamido (e.g., benzenesulfonamido)] aliphatic hydrocarbon sulfonamido (e.g., alkane sulfonamido) which may have at least one suitable substituent (e.g., hydroxy, carboxy, halogen);

substituted ureido

[e.g., acyl ureido (e.g., N'-aroylureido, etc.)]

substituted aminoxy

such as acylaminoxy [e.g., aliphatic acylaminoxy which may be substituted by aryloxy (e.g., aryloxyalkanoylaminoxy)], alkylidenaminoxy which may be substituted by aryl, heterocyclic radical, (e.g., alkylidenaminoxy, heterocyclic-alkylidenaminoxy, aralkylidenaminoxy), which may have at least one suitable substituent (e.g., carboxy, or its derivative alkoxy), in which, the aryl and heterocyclic ring may be additionally substituted by at least one suitable substituent selected from carboxy or its derivative (e.g., the salt, the ester), amino or protected amino, hydroxy or protected hydroxy, halogen, nitro, oxo, carbazoyl, acyl [e.g., alkanoyl (e.g., formyl, alkanoyl], aliphatic radical (e.g., alkyl), aliphatic radical-oxy (e.g., alkoxy), aryl, aryl-aliphatic radical (e.g., aralkyl) or acylamino (e.g., alkanoylamino); and the aliphatic moiety or radical may comprise 1—8 carbon atoms, preferably 1—4 carbon atoms and may be additionally substituted by at least one suitable substituent selected from carboxy or its derivative (the salt, the ester) amino or protected amino, azido, nitro, halogen, hydroxy or sulfo.

Further, in the above definition, heterocyclic radical is mentioned in the above explanation, and particularly is intended to mean mono-aliphatic or aromatic heterocyclic radical, which may be 5—7 membered heterocycle containing at least one hetero atom selected from oxygen, nitrogen and sulfur, and poly-aliphatic or aromatic heterocyclic radical, for example, benzene-fused heterocyclic radical, heterocycle-fused aryl, radical or heterocycle-fused heterocyclic radical, in which the heterocycle may be 5—7 membered heterocycle containing at least one heteroatom selected from oxygen, nitrogen and sulfur.

Aa is a group of the formula:

$$\begin{array}{l}—CH—A_a^2 \\ \;\;\;| \\ \;\;\;A_a^3\end{array}$$

in which

A_a^2 is phenyl which may be substituted by at least one substitutent selected from hydroxy, amino, nitro, alkyl, alkoxy, aralkoxy, alkylthio and halogen, and

A_a^3 is carboxy or its derivatives,

provided that, when

R_1 is 2-[4-(3-amino-3-carboxypropoxy)phenyl]-2-hydroxyiminoacetamido,

A is not α-carboxy-4-hydroxybenzyl or its derivative at the carboxy group.

The object compounds (I) of the present invention may be formulated for administration in any convenient way by analogy with other antibiotic.

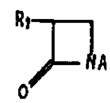
Thus, the composition of present invention can be used in the form of pharmaceutical preparation, for examples, in solid, semisolid or liquid form, which contains the active object compound (I) of the present invention in admixture with a pharmaceutical organic or inorganic carrier or excipient suitable for external or parenteral applications. The active ingredient may be compounded, for example, with usual carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, aqueous suspensions, and other form suitable for use. The carriers which can be used are glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes. The compositions of the present invention can also contain preserving or bacteriostatic agents thereby keeping the active ingredient in the desired preparations stable in activity. The active object compound (I) of the present invention is included in the composition of the present invention in an amount sufficient to produce the desired therapeutic effect upon the bacterially infected process or condition. While the dosage or therapeutically effective quantity of the compound (I) of the present invention varies from and also depends upon the age and condition of each individual patient to be treated, a daily dose of 0.5—5 g, preferably 1—2 g/day of the active ingredient is generally given for treating diseases against which the compound (I) of the present invention are useful.

The following examples are given for the purpose of illustrating the present invention.

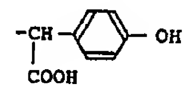
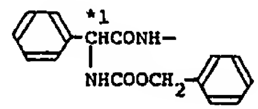
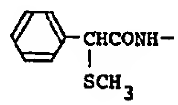
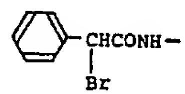
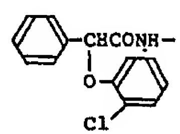
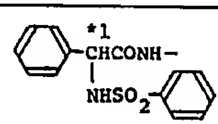
Example 1.

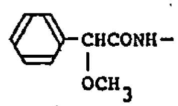
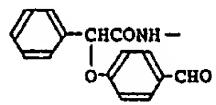
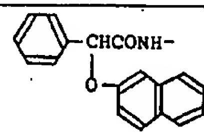
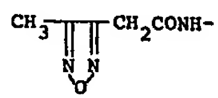
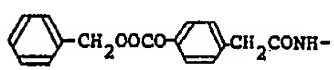
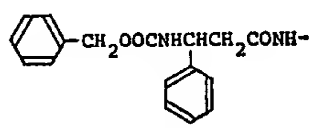
3-Amino-1-(α-carboxy-4-hydroxybenzyl)-2-azetidinone (hereinafter referred to 3-aminolactacillanic acid) (0.94 g.) was suspended in water (10 ml.), whereafter to the suspension was added sodium bicarbonate (0.80 g.). To the solution was added acetone (10 ml.) and then the solution was cooled to −7°C, whereafter acetone (5 ml.) containing 2-phenylacetyl chloride (0.80 g.) was added to the solution. The reaction mixture was stirred at the same temperature for 2 hrs, and then the acetone was distilled off under reduced pressure. The remaining aqueous layer was washed with ether, and then adjusted to pH 2 with 10% hydrochloric acid, whereafter twice extractions were carried out with ethyl acetate (15 ml.). The extracts obtained were combined, and washed with water and a sodium chloride-saturated-aqueous solution, respectively, whereafter it was dried over anhydrous magnesium sulfate. The solvent was distilled off from the extract and the residue obtained was treated with a small amount of a mixture of ethyl acetate and ether to give 3-(2-phenylacetamido)-lactacillanic acid (0.53 g.). Mp 134 to 141°C.

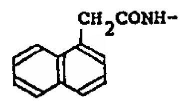
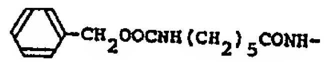
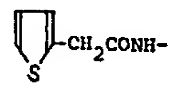
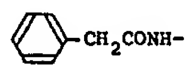
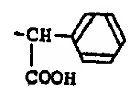
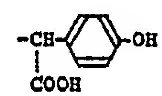
The following compounds were obtained in substantially the similar manner as described above.

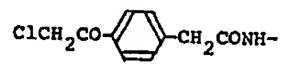
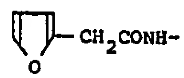
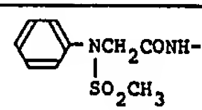
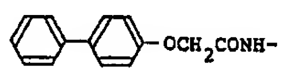
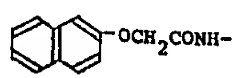


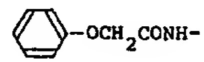
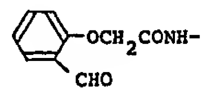
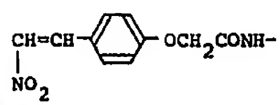
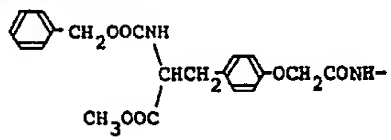
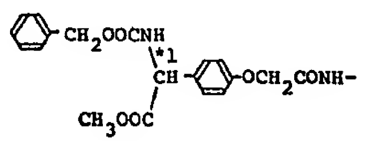
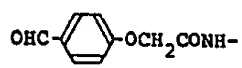
(I)

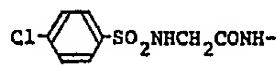
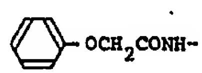
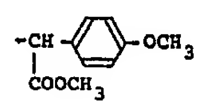
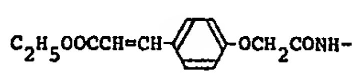
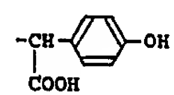
Example	R_1 (note 1)	A	mp (°C) (dec.)
2	$CH_3CH_2CH(Br)CONH-$		156 - 158
3		"	146 - 148
4		"	159 - 162
5		"	173 - 175
6		"	(sodium salt) 195 - 197
7		"	(sodium salt) 186 - 189

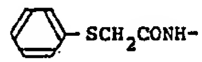
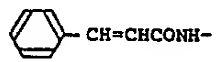
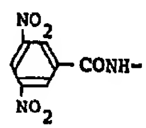
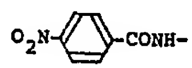
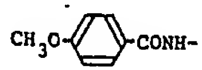
8		"	181 - 185
9		"	95 - 96
10		"	174 - 175
11		"	167 - 168
12		"	85 - 89
13		"	169 - 173

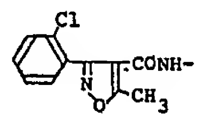
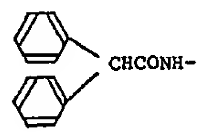
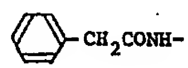
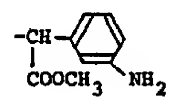
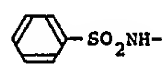
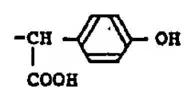
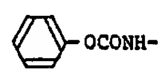
14		"	199 - 201
15		"	I.R. ν cm^{-1} (Nujol) (Trade Mark): 1730, 1660
16			180 - 183
17		$-CH_2COOH$	144 - 145
18	"		174 - 175
19	$HOOCCH_2CH_2CONH-$		(disodium salt) I.R. ν cm^{-1} (KBr): 1740 1660, 1585

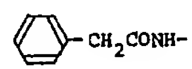
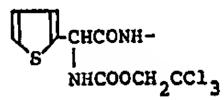
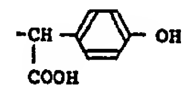
20		"	136 - 139
21		"	171 - 173
22	$C_2H_5OCOCONH-$	"	210 - 213
23		"	116 - 119
24	CH_3OCH_2CONH-	"	125 - 129
25	$CH_3SO_2NHCH_2CONH-$	"	(sodium salt) 160 - 164
26		"	195 - 198
27		"	143 - 146

28		"	180 - 184
29		"	181 - 183
30		"	134 - 135
31		"	136 - 140
32		"	80 - 85
33		"	145 - 146

34		"	168 - 173
35	CH_2=$CHCH_2SCH_2CONH$-	"	178 - 183
36	CH_3SCH_2CONH-	"	154 - 155
37		"	137 - 140
38	N_3CH_2CONH-	"	171 - 173
39	$BrCH_2CONH$-	"	145 - 150
40			N.M.R. δ ppm ($CDCl_3$): 3.14(1H,d,d,J=3Hz,6Hz), 3.76 (3H,s), 3.81(3H,s), 3.96(1H, t,J=6Hz,6Hz), 4.46(2H,s), 5.08(1H,heptet), 5.59(1H, s), 6.80 - 7.40(9H,m)
41			109 - 110

42	$ClCH_2CONH-$	"	165 - 167
43		"	183 - 185
44		"	192 - 193
45		"	179 - 180
46		"	170 - 175
47		"	195 - 197
48		"	160 - 165

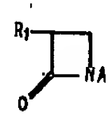
49		"	(sodium salt) I.R. ν cm^{-1} (Nujol): 1735, 1655, 1610
50	$Cl_2CHCONH-$	"	178 - 183
51		"	135 - 140
52			I.R. ν cm^{-1} ($CHCl_3$): 1755 1745 1675
53			172 - 174
54		"	198 - 200

55		-H	178 - 181
56			171 - 176

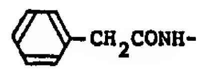
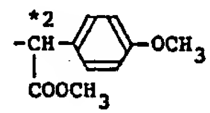
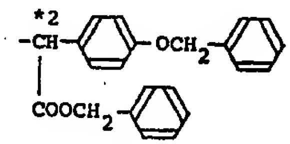
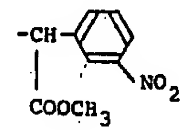
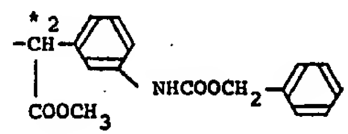
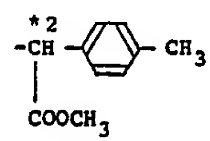
Example 57.

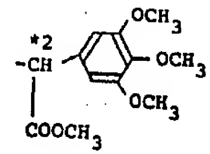
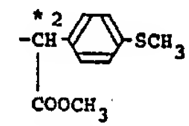
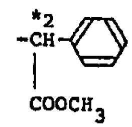
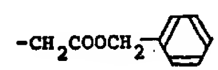
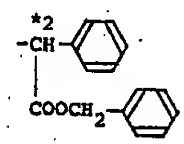
N-phenylglycyl chloride hydrochloride (492 mg.) was suspended in methylene chloride (10 ml.), and the suspension was cooled to −15°C. To the suspension were added all at once a solution prepared by dissolving 3-aminolactacillanic acid (472 mg.) and, N,O-bis(trimethylsilyl)acetamide (2.03 g.) in methylene chloride (17 ml.). The mixture was stirred for 1 hour, keeping the reaction temperature of the mixture at 0 to −10°C, and then stirred for 1.5 hrs. after removing the cooling bath. The methylene chloride was distilled off from the reaction mixture, and the residue obtained was dissolved in ethyl acetate. The solution was washed with water and a sodium chloride-saturated-aqueous solution respectively, and dried. The solvent was distilled off from the solution, and to the residue was added a small amount of acetone to give crystals of 3-(N-phenylglycinamido)]lactacillanic acid (116 mg.). Mp 194 to 194.5°C. The filtrate was allowed to stand under cooling to give crystals of the same object compound (60 mg.). Mp 193 to 194.5°C. Total yield was 176 mg.

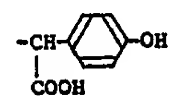
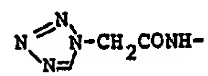
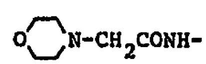
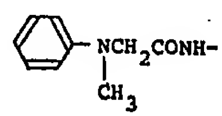
The following compounds were obtained in substantially the similar manner as described above.

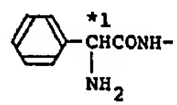
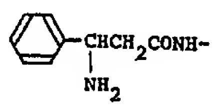
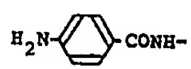
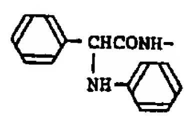
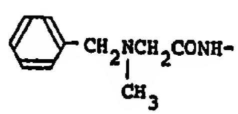


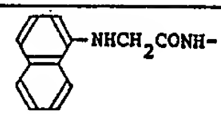
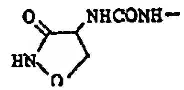
(I)

Example	R_1 (note 1)	A	mp (°C) (dec.) (note 2)
58			(D isomer) 145 - 146 (L isomer) I.R. ν cm^{-1} ($CHCl_3$): 1760, 1740, 1680
59	"		(D isomer) 129 - 130 (L isomer) I.R. ν cm^{-1} (liquid film): 3300, 1760 - 1740, 1665
60	"		I.R. ν cm^{-1} ($CHCl_3$): 1765, 1745, 1680, 1525, 1350
61	"		isomer A) I.R. ν cm^{-1} ($CHCl_3$): 1760(s) 1745, 1710 (s), 1675 isomer B) I.R. ν cm^{-1} ($CHCl_3$): 1755(s) 1745, 1710(s), 1675
62	"		isomer A) 148 isomer B) I.R. ν cm^{-1} ($CHCl_3$): 1755, 1745, 1675

63	"		isomer A) 138 - 140 isomer B) N.M.R. δ ppm($CDCl_3$): 3.54(2H, m), 3.59(2H,s), 3.73(3H,s), 3.82(9H,s), 4.96(1H,m), 5.45(1H,s), 6.13(1H,d,J=8Hz), 6.43(2H,s), 7.10 - 7.45(5H,m)
64	"		isomer A) 115 - 117 isomer B) 157 - 159
65	"		isomer A) 138 - 140 isomer B) I.R. ν cm^{-1}($CHCl_3$): 1770, 1745, 1678
66	"	$-CH_2COOC_2H_5$	104 - 105
67	"		114 - 115
68	"		isomer A) 96 - 98 isomer B) I.R. ν cm^{-1}($CHCl_3$): 1760, 1740(s), 1678

69	"	$-CH_2CN$	175 - 179
70	NC-C-CONH- ‖ N-OH		(sodium salt) 240 - 245
71		"	177 - 181
72	H_2NCH_2CONH-	"	I.R. ν cm^{-1} (Nujol): 1730, 1665, 1610
73		"	201 - 203
74		"	198 - 199
75	$(CH_3)_3CCONH-$	"	187 - 188

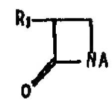
76		"	193 - 196
77		"	179 - 185
78		"	190 - 194
79		"	97 - 101
80		"	154 - 157

81		"	182 - 185
82		"	189 - 198

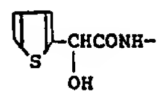
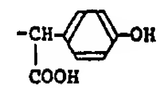
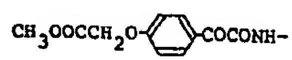
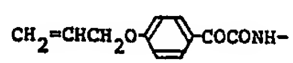
Example 83.

A mixture of N,N-dimethylformamide (320 mg.) and thionyl chloride (780 mg.) was heated for 30 minutes at 40 to 50°C, and the excess of the thionyl chloride was distilled off from the mixture, and the residue obtained was suspended in methylene chloride (10 ml.). To the suspension was added 4-hydroxyphenylglyoxylic acid (370 mg.) under cooling at −15 to −20°C, and the mixture was stirred for 15 minutes. After the reaction temperature of the mixture was elevated to −5 to −10°C, the mixture was stirred for 10 minutes to obtain a clear solution containing 4-hydroxyphenylglyoxyloyl chloride. Subsequently, the solution was cooled to −45 to −50°C, and to the solution was added dropwise a solution of triethylamine (440 mg.) and methylene chloride (2 ml.) during 5 minutes, and then the reaction mixture was stirred for 30 minutes. A solution, prepared by subjecting 3-aminolactacillanic acid (470 mg.) and N,O-bis(trimethylsilyl)acetamide (1.2 g.) to a dissolution in dried methylene chloride (10 ml.) at room temperature for 1 hour while stirring was added all at once to the solution, keeping the temperature at −45 to −50°C. The reaction mixture was stirred for 30 minutes, and then stirred for 1.5 hrs., elevating the reaction temperature to room temperature slowly after removing the cooling bath. The methylene chloride was distilled off from the reaction mixture, and the residue obtained was dissolved in 5% sodium bicarbonate aqueous solution (20 ml.). The solution was washed with ethyl acetate (10 ml.) twice, and ethyl acetate (50 ml.) was added to the solution, whereafter the aqueous layer was adjusted to pH 1 with 5% hydrochloric acid while shaking enough. The ethyl acetate layer was separated out, and the aqueous layar was extracted with ethyl acetate (20 ml.) twice. The ethyl acetate layers were combined, washed with a sodium chloride-saturated-aqueous solution and dried over anhydrous magnesium sulfate. The solvent was distilled off from the solution to give crude crystals of 3-(4-hydroxyphenylglyoxyloylamino)lactacillanic acid (460 mg.). This product (760 mg.) prepared by the same manner as mentioned above was dissolved in ethyl acetate (3 ml.), and the solution was subjected to column chromatography using silica gel. The fractions containing the object compound were collected by eluting with ethyl acetate. The residue, obtained by distilling off the solvent from the eluate, was dissolved in acetone, and then an acetone solution of sodium 2-ethylhexanoate was added to the solution to give the solution of the sodium salt of the object compound, and then the acetone was distilled off from the solution. The residue was powdered by adding ether, and the powder was collected by filtration and washed with acetone to give 3-(4-

hydroxyphenylglyoxyloylamino)lactacillanic acid sodium salt (170 mg.). Mp 220 to 225°C. The following compounds were obtained in substantially the similar manner described above.



(I)

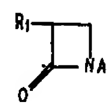
Example	R_1	A	mp (°C) (dec.)
84			187 - 191
85		"	203 - 204
86	$CH_3COCONH-$	"	162 - 166
87		"	(sodium salt) I.R. ν cm^{-1} (Nujol): 1735, 1655, 1595
88		"	151 - 157

Example 89.

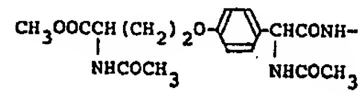
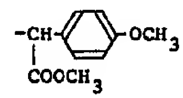
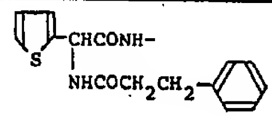
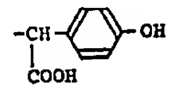
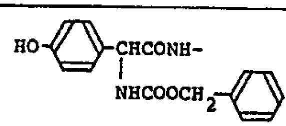
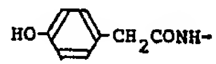
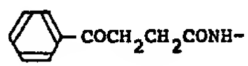
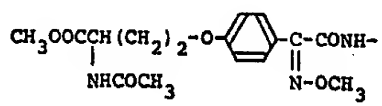
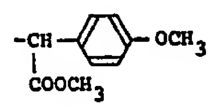
Sodium bicarbonate (0.453 g.) was dissolved in water (10 ml.), and the solution was cooled to 5°C. To the solution was added 3-aminolactacillanic acid (0.427 g.), and then acetone (10 ml.) was added to the solution. To the solution was added dropwise an acetone (5 ml.) solution of butyric acid anhydride (0.38 g.) for 5 minutes. Sodium bicarbonate (0.04 g.) was added to the reaction mixture and then stirred for 1.5 hrs. at 5°C. The acetone was distilled off from the reaction mixture, and the aqueous layer was washed with ether, and then adjusted to pH 1 to 2 with 10% hydrochloric acid. The aqueous layer was extracted with ethyl acetate (30 ml.) twice respectively. The extracts were combined, washed with water (50 ml.) and then washed with a sodium chloride-saturated-aqueous solution, and dried over anhydrous magnesium sulfate. The solvent was concentrated to give crystals of 3-butyramidolactacillanic acid (112 mg.). Mp 178 to 178.5°C (dec.).

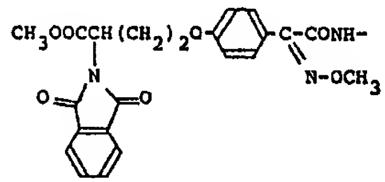
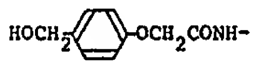
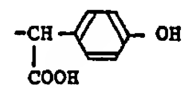
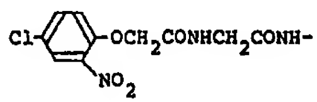
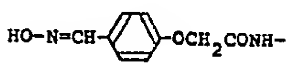
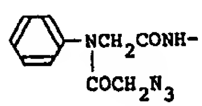
Example 90.

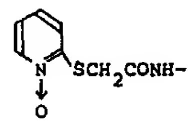
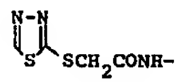
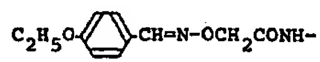
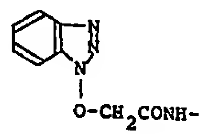
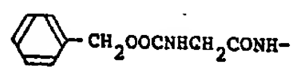
Pivaloyl chloride (0.350 g.) was dissolved in methylene chloride (15 ml.), and to the solution was added a solution prepared by dissolving 4-methoxyphenylglyoxylic acid (0.520 g.) and triethylamine (0.290 g.) in methylene chloride (10 ml.). The mixed solution was reacted for 1 hour to prepare a mixed acid anhydride solution with 4-methoxyphenylglyoxylic acid and pivalic acid. On the other hand, N,O-bis(trimethylsilyl)-acetamide (2.3 g.) was added to a suspension prepared by suspending 3-aminolactacillanic acid (0.680 g.) in methylene chloride (10 ml), and the suspension was stirred for 1 hour at ambient temperature. To the solution obtained was added the mixed acid anhydride solution obtained above, and the reaction mixture was reacted for 2 hrs., keeping the reaction temperature at −10 to −15°C. The methylene chloride was distilled off from the reaction mixture, and the residue obtained was dissolved in ethyl acetate. The solution was washed with 5% hydrochloric acid and a sodium chloride-saturated-aqueous solution, respectively, and then dried over anhydrous magnesium sulfate. The solvent was distilled off from the solution, and diisopropyl ether (about 30 ml.) was added to the residue, and then the mixture was stirred for 1 hour. The precipitating material obtained was collected by filtration to give the powder (1.14 g.). This powder was dissolved in ethyl acetate (30 ml.), and the solution was treated with an activated carbon (0.11 g.) and filtered. The filtrate was concentrated to the volume of about 2 ml., and crystals were obtained by scrubbing the wall of the vessel containing the solution. The crystals were collected by filtration and recrystallized from a small amount of ethyl acetate to give crystals of 3-(4-methoxyphenylglyoxyloylamino)lactacillanic acid (0.16 g.). Mp 178 to 181°C (dec.). The following compounds were obtained in substantially the similar manner as described above.

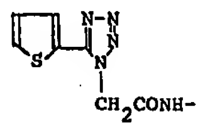


(I)

Example	R_1 (note 1)	A	mp (°C) (dec.)
91			I.R. ν cm^{-1} ($CHCl_3$): 1745, 1667
92			(sodium salt) 224 - 227
93		"	I.R. ν cm^{-1} (Nujol): 1760, 1730, 1680
94		"	171 - 176
95		"	157 - 161
96			N.M.R. δ ppm($CDCl_3$): 1.95(3H,s), 2.25(2H,m), 3.15(1H,d,d,J=3Hz), 6Hz), 3.70(3H,s), 3.74(3H,s), 3.78(3H,s), 3.89(3H,s), 3.96 (2H,t,J=6Hz), 4.70(1H,q,J=8Hz), 4.92(1H,m), 5.52(1H,s), 6.75 (2H,d,J=9Hz), 6.86(2H,d,J=9Hz), 7.20(2H,d,J=9Hz), 7.45(2H,d, J=9Hz)

97		"	N.M.R. δ ppm($CDCl_3$): 2.70(2H,m), 3.15(1H,d,d,J=3Hz,6Hz),3.7(1H, m), 3.75(6H,s), 3.78(3H,s), 3.88(3H,s), 3.94(2H,m), 5.05 (1H,m), 5.16(1H,t,J=6Hz), 5.56(1H,s), 6.62(2H,d,J=9Hz), 6.84(2H,d,J=9Hz), 7.20(2H, d,J=9Hz), 7.38(2H,d,J=9Hz), 7.74(4H,m)
98			182 - 185
99		"	149 - 153
100		"	150 - 155
101		"	176 - 180

102		"	221 - 225
103		"	163 - 167
104		"	130 - 135
105		"	179 - 181
106		"	(sodium salt) I.R. ν cm^{-1} (Nujol): 1740, 1675, 1610

107		"	197.5 - 198
108	CH_3SCH=CHCONH-	"	174 - 177

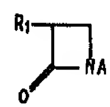
Example 109.

3-Aminolactacillanic acid (0.944 g.) was suspended in dried methylene chloride (60 ml.), and to the suspension were added N,O-bis(trimethylsilyl)acetamide (7.0 g.) and N,N-dimethylformamide (0.7 ml.), whereafter the mixture was stirred for 2 hrs. at ambient temperature. On the other hand, to a dried methylene chloride (30 ml.) solution of ethyl chloroformate (0.523 g.) was added dropwise a dried methylene chloride (30 ml.) solution of N-benzyloxycarbonyl-2-(2-thienyl)glycine (1.40 g.) and triethylamine (0.485 g.) during 7 minutes under cooling at −5 to −10°C, and then the mixture was stirred at the same temperature for 20 minutes to prepare a mixed acid anhydride solution. To this solution was added dropwise the solution obtained above during 20 minutes, and then the reaction mixture was stirred for 3 hrs. at the same temperature, and the reaction temperature was slowly elevated to room temperature during 2 hrs. while stirring. The reaction mixture was washed with diluted hydrochloric acid and water, respectively, and then dried. The solution was concentrated to give crystals of 3-[2-(2-thienyl)-N-benzyloxycarbonylglycinamido]lactacillanic acid (1.40 g.).

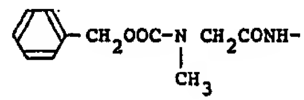
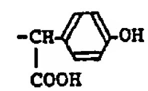
I.R. absorption spectrum,

ν cm^{-1} (liquid film): 1730, 1710, 1650.

The following compound was obtained in substantially the similar manner as described above.



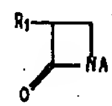
(I)

Example	R_1	A	I.R.
110			I.R. ν cm^{-1} (liquid film): 1740, 1710, 1690, 1650

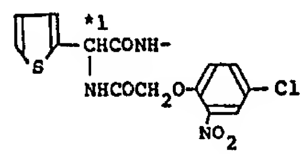
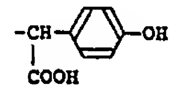
Example 111.

2-(4-Methoxyphenyl)-2-methoxyiminoacetic acid (500 mg.) and N,N'-dicyclohexylcarbodiimide (495 mg.) were dissolved in a mixture of chloroform (9 ml.) and dioxane (3 ml.), and the solution was stirred for 1.5 hrs. under ice-cooling. To the solution was added all at once a solution, prepared by dissolving 3-aminolactacillanic acid (472 mg.) and N,O-bis(trimethylsilyl)acetamide (1.22 g.) in chloroform (10 ml.), and then the reaction cixture was stirred for 4 hrs. at ambient temperature. The solvent was distilled off from the reaction mixture, and to the residue were added a sodium bicarbonate aqueous solution and ethyl acetate. After stirring the mixture, the aqueous layer was separated out, adjusted to pH 1 to 2 with 10% hydrochloric acid and then extracted with ethyl acetate. The extract was washed with water and then dried. The solvent was distilled off from the extract, and ether was added to the residue to give crude crystals. The crystals were collected by filtration and washed with ether to give crystals of 3-[2-(4-methoxyphenyl)-2-methoxyiminoacetamido]lactacillanic acid (150 mg.). Mp 157 to 161°C (dec.).

The following compound was obtained in substantially the similar manner as described above.



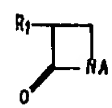
(I)

Example	R_1	A	I.R.
112			(sodium salt) νcm^{-1} (Nujol): 1730 1660 1610

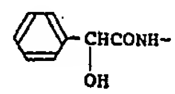
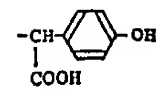
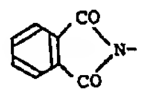
Example 113.

3-Aminolactacillanic acid (0.472 g.) was suspended in methylene chloride (10 ml.), and to the suspension was added N,O-bis(trimethylsilyl)acetamide (1.22 g.) at ambient temperature, and then the solution was cooled to −15°C. To the solution was added dropwise during 25 minutes a methylene chloride (10 ml.) solution of triethylammonium salt of acid anhydride (935 mg.) prepared from 2-phenyl-2-sulfoacetic acid and ethyl chloroformate, and the reaction mixture was stirred for 1 hour at the same temperature and further for 1.5 hrs. at ambient temperature. Water (50 ml.) was added to the reaction mixture and then the aqueous layer was separated out. The aqueous layer was washed with ethyl acetate and adjusted to pH 5 to 6 with an aqueous solution of sodium bicarbonate, and then the solution was filtered. The filtrate was concentrated, and the residue obtained was adsorbed on a column packed with nonionic adsorption resin, Amberlite XAD—4 (trade mark, maker: Rohm and Haas Co., Ltd.) (20 ml), which had been treated in advance with methanol, and the object compound was eluted with water. The eluate was concentrated under reduced pressure, and ethanol was added to the eluate, whereafter the solvent was distilled off from the eluate under reduced pressure. Ethanol was added to the residue to give crystals. The crystals were collected by filtration to give crystals of 3-(2-phenyl-2-sulfoacetamido)lactacillanic acid disodium salt (120 mg.). Further, the filtrate was concentrated, and the oily material obtained was treated with acetone to give powdery crystals of 3-(2-phenyl-2-sulfoacetamido)-lactacillanic acid disodium salt (0.45 g.). Mp 144 to 152°C.

The following compounds were obtained in substantially the similar manner as described above.



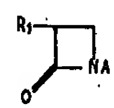
(I)

Example	R_1	A	mp(°C) (dec.)
114			180 - 183
115		"	196 - 199

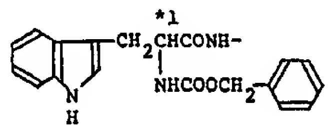
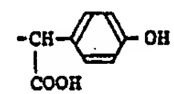
Example 116.

2-(Benzo[d]isoxazol-3-yl)-N-benzyloxycarbonylglycine (652 mg.) and triethylamine (202 mg.) were dissolved in dried tetrahydrofuran (8 ml.). To the solution was added 6-chloro-1-(4-chlorobenzenesulfonyloxy)benzotriazole (690 mg.) while stirring under ice-cooling, and then the solution was stirred at the same temperature for 3 hrs. Keeping the solution under ice-cooling, a solution, prepared by dissolving 3-aminolactacillanic acid (472 mg.) and triethylamine (202 mg.) in a mixed solution of acetone and water (1:1) (10 ml.), was added to the solution. The reaction mixture was stirred for 1 hour, and then the solvent was distilled off from the reaction mixture. To the residue obtained was added water (20 ml.), whereafter ethyl acetate was added to the solution and then the solution was acidified by adding dropwise 1N-hydrochloric acid while shaking. Ethyl acetate layer was separated out, whereafter the aqueous layer was subjected to extraction with ethyl acetate, and the ethyl acetate extracts were combined. The extract was washed with water and then dried over anhydrous magnesium sulfate. The solvent was distilled off from the solution to obtain the residue (1.2 g.). The residue was subjected to column chromatography using silica gel and elution was conducted with ethyl acetate containing 10% methanol (500 ml.) to obtain the fractions containing the object compound. The residue obtained by concentrating the eluate was treated with ether to give crystals of 3-[2-(benzo[d]isoxazol-3-yl)-N-benzyloxycarbonylglycinamido]lactacillanic acid (180 mg.). Mp 159 to 168°C.

The following compound was obtained in substantially the similar manner as described above:



(I)

Example	R_1 (note 1)	A	mp (°C) (dec.)
117			235 - 240

Example 118.

3-Aminolactacillanic acid (0.472 g.) was suspended in water (20 ml.), and to the suspension was added sodium bicarbonate (0.420 g.). Acetone (20 ml.) was added to the solution, and the solution was cooled to 0 to 5°C. To the solution was added dropwise an acetone (2 ml.) solution containing phenyl isocyanate (0.286 g.), and then the solution was stirred for 2.5 hrs. at the same temperature. The acetone was distilled off from the reaction mixture, and then the residue obtained was filtered to remove insoluble materials.

The aqueous solution obtained was washed with ethyl acetate, and then adjusted to pH 1 with 10% hydrochloric acid, whereafter, extraction was conducted with ethyl acetate. The ethyl acetate layer obtained was washed with water and then dried over anhydrous magnesium sulfate. The solvent was distilled off from the solution to give the crystalline residue. The residue was washed with diisopropyl ether and collected by filtration to give crystals of 3-(N'-phenylureido)lactacillanic acid (0.470 g.). Mp 167 to 172°C.

Example 119.

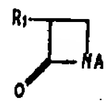
Guanidinocarbohydrazide dihydrochloride (0.38 g.) was dissolved in water (2 ml.), and to the solution was added sodium nitrite (0.14 g.) under cooling at 0 to 5°C, and then the solution was stirred for 15 minutes to prepare a solution of guanidinocarbonylazide. On the other hand, 3-aminoactacillanic acid (0.240 g.) was suspended in water (7 ml.), and to the suspension was added sodium bicarbonate (0.170 g.). The aqueous solution was cooled to 0 to 5°C, and to the solution was added dropwise the solution of guanidinocarbonylazide prepared above during 10 minutes, and then the reaction mixture was stirred for 2 hrs. The reaction mixture was washed with ethyl acetate (10 ml.) and concentrated until the remaining solution became transparent, and then the ethyl acetate saturated in the aqueous layer was distilled off completely to precipitate crystals. The solution containing the crystals was allowed to stand for a while

and the crystals were collected by filtration to give crystals of 3-(guanidinocarbonamido)lactacillanic acid (0.15 g.). Mp 206 to 210°C.

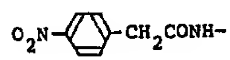
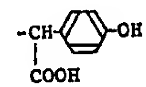
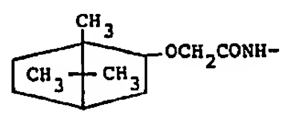
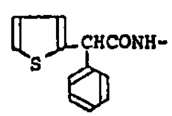
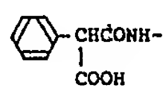
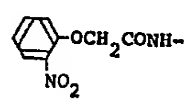
Example 120.

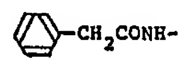
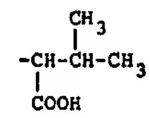
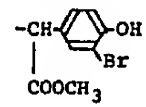
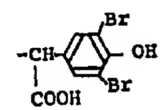
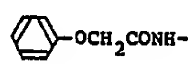
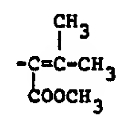
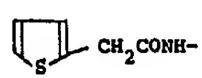
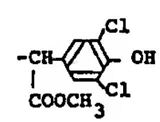
A solution containing 2-phenyl-N-(2,2,2-trichloroethoxycarbonyl)glycine (1.42 g.) and thionyl chloride (15 ml.) was heated for 1 hour under reflux. The excess of the thionyl chloride was distilled off from the solution under reduced pressure, and the residue obtained was dissolved in acetone. To the solution was added dropwise a solution containing 3-aminolactacillanic acid (1.0 g.), sodium bicarbonate (0.9 g.), water (40 ml.) and acetone (40 ml.) under cooling at 0 to 5°C. The acetone was distilled off from the reaction mixture under reduced pressure, and the remaining solution was washed with ethyl acetate. The solution was adjusted to pH 1 to 2 with 10% hydrochloric acid, and then extracted with ethyl acetate. The ethyl acetate layer was separated out and dried over anhydrous magnesium sulfate. The solvent was distilled off from the ethyl acetate solution, and the residue (2.1 g.) obtained was dissolved in ether. The ether solution was concentrated to give a residue. The residue was washed with diisopropyl ether to give crystals of 3-[2-phenyl-N-(2,2,2-trichloroethoxycarbonyl)glycinamido]lactacillanic acid (1.69 g.). Mp 130 to 132°C (dec.).

The following compounds were obtained in substantially the similar manner as described above.



(I)

Example	R_1	A	mp(°C) (dec.)
121			234 - 236
122		"	106 - 109
123		"	139 - 143
124		"	(disodium salt) 209 - 214
125		"	(sodium salt) 116

126			106 - 109
127	"		151 - 153
128	"		161 - 162
129			155.5 - 156.5
130			I.R. ν cm^{-1} (liquid film) 3270, 1760 1735, 1665

Example 131.

3-Aminolactacillanic acid (700 mg.) was suspended in dried methylene chloride (15 ml.), and to the suspension was added N,O-bis(trimethylsilyl)acetamide (3.6 g.), and then the mixture was stirred for 3 hrs. The solution was cooled to −50 to −40°C, and to the solution was added all at once 2-(2-pyridyloxy)acetyl chloride hydrochloride (630 mg.), and the reaction mixture was stirred for 20 minutes at the same temperature. Elevating slowly the reaction temperature to −10°C during 40 minutes, the reac-

tion mixture was stirred for 1 hour at the same temperature and further for 1 hour under ice-cooling. The methylene chloride was distilled off from the reaction mixture, and to the residue was added a solution containing 5% sodium bicarbonate aqueous solution (25 ml.) and ethyl acetate (30 ml.). The aqueous layer was separated out, and then washed with ethyl acetate. The aqueous layer was adjusted to pH 3 with 10% hydrochloric acid under ice-cooling, and then the aqueous solution was extracted with ethyl acetate. The ethyl acetate layer was separated out, and the remaining aqueous layer was adjusted to pH 1 to 2 with 10% hydrochloric acid, and then the aqueous solution was extracted with ethyl acetate several times. These ethyl acetate layers and the ethyl acetate layer obtained above were combined, and the solution was washed with a sodium chloride-saturated-aqueous solution, and then dried over anhydrous magnesium sulfate. The solvent was distilled off from the ethyl acetate solution, and the residue (330 mg.) obtained was powdered with ether. The powder was washed with acetone to give crystals of 3-[2-(2-pyridyloxy)acetamido]lactacillanic acid (130 mg.). Mp 192.5 to 193°C (dec.).

Example 132.

A mixture of N,N-dimethylformamide (292 mg.) and thionyl chloride (710 mg.) was heated for 30 minutes at 50°C. The excess of the thionyl chloride was distilled off from the mixture to give a residue. The residue was washed with ether. Methylene chloride (7 ml.) was added to the residue and then the solution was cooled to 0 to 5°C, whereafter a solution prepared by dissolving 2-(5,6-dihydro-2H-pyran-3-yl)glycolic acid (455 mg.) in methylene chloride (5 ml.), was added dropwise to the solution. To the reaction mixture was added dropwise a methylene chloride (5 ml.) solution of triethylamine (600 mg.) during 10 minutes under cooling at −50°C, and the solution was stirred for 30 minutes at the same temperature. The solution was added all at once to a mixture of 3-aminolactacillanic acid (472 mg.), N,O-bis(trimethylsilyl)acetamide (1.22 g.) and methylene chloride (10 ml.) which had been stirred for 2 hrs. at room temperature previously. The reaction mixture was stirred for 2 hrs. at −50°C, and further stirred for 2 hrs., elevating slowly the reaction temperature to 0°C. The solvent was distilled off from the reaction mixture, and to the remaining solution were added a sodium bicarbonate aqueous solution and ethyl acetate. The aqueous layer obtained was adjusted to pH 1 to 2 with 10% hydrochloric acid, and then the solution was extracted with ethyl acetate. The extract was washed with water, and dried over anhydrous magnesium sulfate, and then the solvent was distilled off from the extract to give crystals of 3-[2-(5,6-dihydro-2H-pyran-3-yl)glycolamido]lactacillanic acid (80 mg.).

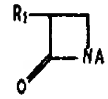
I.R. absorption spectrum,

ν cm^{-1} (Nujol): 1740, 1685, 1660.

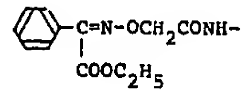
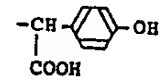
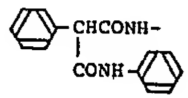
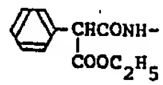
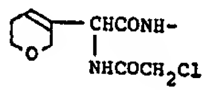
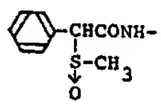
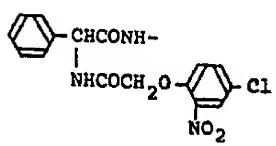
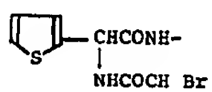
Example 133.

To the solution of methylene chloride (10 ml.) containing ethyl chloroformate (216 mg.) was added dropwise a mixture of 2-(2-bromoacetamido)-2-phenylacetic acid (576 mg.), triethylamine (200 mg.), N,N-dimethylbenzylamine (one drop) and methylene chloride (8 ml.) under cooling at −30°C, and then the reaction mixture was stirred for 30 minutes at the same temperature. A mixture of 3-aminolactacillanic acid (472 mg.), N,O-bis(trimethylsilyl)acetamide (1.2 g.), methylene chloride (10 ml.) and N,N-dimethylformamide (1 ml.), which had been stirred for a while at room temperature and cooled to 0°C was added all at once to the reaction mixture, keeping the temperature of the reaction mixture at −30°C. The reaction mixture was stirred for 2 hrs. at −25°C and then stirred for 1 hour, elevating slowly the reaction temperature to 0°C. The reaction mixture was concentrated, and to the residue obtained were added ethyl acetate and water. And then the mixture was adjusted to pH 1 to 2 with 10% hydrochloric acid. The ethyl acetate layer was separated out, washed with water, dried over anhydrous magnesium sulfate and then concentrated. The residue obtained was washed with diisopropyl ether, and then powdered with ethyl acetate to give 3-[2-(2-bromoacetamido)-2-phenylacetamido]lactacillanic acid (400 mg.). Further, the same compound (188 mg.) was recovered from the mother liquor. Total yield was 588 mg. Mp 156 to 161°C (dec.).

The following compounds were obtained in substantially the similar manner as described above.



(I)

Example	R_1	A	mp(°C) (dec.)
134			(sodium salt) 157 - 160
135		"	(sodium salt) 183 - 187
136		"	103 - 107
137		"	211 - 217
138		"	I.R. ν cm^{-1} (Nujol) 1740, 1720, 1665
139		"	77 - 81
140		"	147 - 150

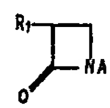
Example 141.

A mixture of N-phenylimidinodiacetic acid (537 mg.), N,N'-dicyclohexylcarbodiimide (495 mg.), chloroform (9 ml.) and dioxane (3 ml.) was stirred for 1.5 hrs. under ice-cooling. The insoluble materials were filtered off from the solution, and to the filtrate was added all at once a mixture of 3-aminolactacillanic acid (472 mg.), methylene chloride (10 ml.) and N,O-bis(trimethylsilyl)acetamide (1.2 g.), and then the reaction mixture was stirred for 4 hrs. at room temperature. The solvent was distilled off from the reaction mixture, and the residue was dissolved in ethyl acetate, and to the solution was added a sodium bicarbonate aqueous solution. The mixture was adjusted to pH 4.0 with 10% hydrochloric acid, and the ethyl acetate layer was separated out. The remaining aqueous layer was adjusted to pH 1 to 3 with 10% hydrochloric acid, and the aqueous solution was extracted with ethyl acetate. The ethyl acetate layers were combined, washed with water and dried, and then the solvent was distilled off from the solution to give crystals of 3-(N-carboxymethyl-N-phenylglycinamido)lactacillanic acid (260 mg.). Mp 142.5 to 145°C (dec.).

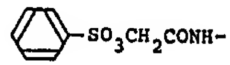
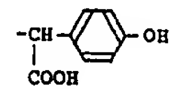
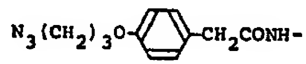
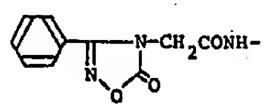
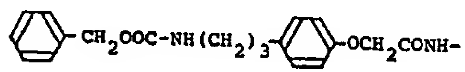
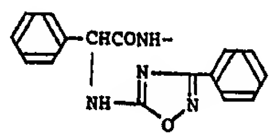
Example 142.

A solution, prepared by dissolving 2-[4-(3-bromopropoxy)phenyl]acetic acid (300 mg.) and thionyl chloride (300 mg.) in chloroform (2 ml.), was heated for 2 hrs. under reflux. The solvent and the excess of the thionyl chloride were distilled off from the solution and the residue obtained was dissolved in dried acetone (1 ml.) The solution was added dropwise to a solution, prepared by dissolving 3-aminolactacillanic acid (240 mg.) and sodium bicarbonate (210 mg.) in a mixture of water (10 ml.) and acetone (10 ml.), under cooling at 0 to 5°C while stirring. The reaction mixture was stirred for 45 minutes at the same temperature. The acetone was distilled off from the reaction mixture, and to the remaining aqueous layer was added ethyl acetate (30 ml.). The mixture was adjusted to pH 1 with 10% hydrochloric acid. The ethyl acetate layer was separated out, and then the aqueous layer was extracted with ethyl acetate (20 ml.). The ethyl acetate layers were combined and washed with a sodium chloride-saturated-aqueous solution, and then dried over anhydrous magnesium sulfate. The solvent was distilled off from the solution, and the residue (510 mg.) obtained was washed with ether to give crystals of 3-[2-{4-(3-bromopropoxy)phenyl}acetamido]lactacillanic acid (420 mg.). Mp 120 to 123°C (dec.).

The following compounds were obtained in substantially the similar manner as described above.



(I)

Example	R_1	A	mp(°C) (dec.)
143			142.5 - 144
144		"	113 - 116
145		"	128 - 132
146		"	142 - 146
147		"	I.R. ν cm^{-1} (Nujol): 1738, 1680, 1618

Example 148.

A mixture of 3-aminolactacillanic acid (472 mg.), N,O-bis(trimethylsilyl)acetamide (1.2 g.), methylene chloride (10 ml.) and N,N-dimethylformamide (1 ml.) was stirred for 1 hour at room temperature. The solution was cooled to 0 to 5°C, and to the solution was added dropwise a methylene chloride (3 ml.) solution containing hexadecanoyl chloride (548 mg.), whereafter the reaction mixture was reacted for 1.5 hrs. at the same temperature and further for 30 minutes at ambient temperature. The reaction mixture was concentrated, and to the remaining solution were added ethyl acetate and water, and then the mixture was adjusted to pH 1 to 2 with 10% hydrochloric acid. The ethyl acetate separated out was washed with water and then dried over anhydrous magnesium sulfate. The solution was concentrated to give crude 3-hexadecanoylaminolactacillanic acid (0.95 g.). Furthermore, the product (600 mg.) was subjected to column chromatography using silica : gel and elution was conducted with ethyl acetate. The solvent was distilled off from the eluate to give the purified object compound (110 mg.). Mp 157 to 161°C (dec.).

Example 149.

To a solution of 2-[N-(2-thenyliden)aminooxy]-2-phenylacetic acid (400 mg.), triethyl amine (155 mg.) and tetrahydrofuran (10 ml.) was added dropwise a solution, prepared by dissolving pivaloyl chloride (184 mg.) in tetrahydrofuran (3 ml.), during 5 minutes under cooling at −2 to 0°C, and the mixture was stirred for 30 minutes. The solution was added all at once to a solution of 3-aminolactacillanic acid (320 mg.), N,O-bis(trimethylsilyl)acetamide (825 mg.) and methylene chloride (10 ml.) under cooling at −30°C, and the reaction mixture was reacted for 2.5 hrs., elevating slowly the reaction temperature to 10°C. The solvent was distilled off from the reaction mixture, and to the remaining solution were added a sodium bicarbonate aqueous solution and ethyl acetate. The aqueous layer separated out was adjusted to pH 1 to 2 with 10% hydrochloric acid and then extracted with ethyl acetate. The extract was washed with water and dried, and then the solvent was distilled off from the solution to give residues (300 mg.). The residues were dissolved in acetone and then sodium 2-ethylhexanate was added to the solution to give crystals of 3-[2-{N-(2-thenyliden)aminooxy]-2-phenylacetamido]lactacillanic acid sodium salt (160 mg.).

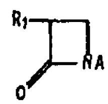
I.R. absorption spectrum,

ν cm^{-1} (Nujol): 1730, 1650, 1600.

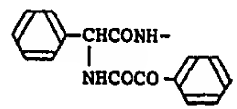
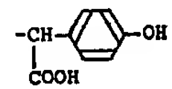
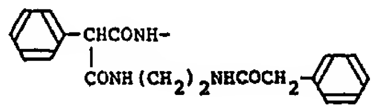
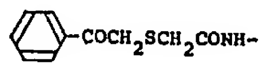
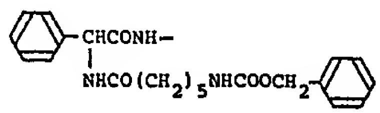
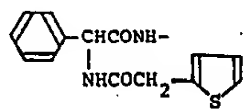
Example 150.

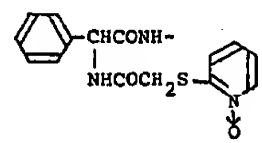
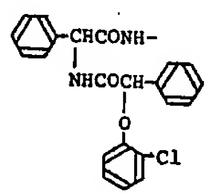
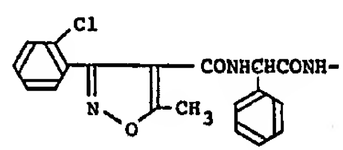
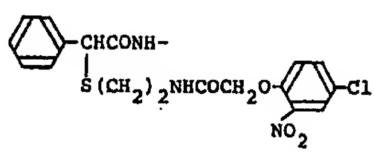
3-Aminolactacillanic acid (355 mg.), N,O-bis(trimethylsilyl)acetamide (0.92 g.) and N,N-dimethylformamide (0.23 ml.) were added to methylene chloride (7 ml.), and the solution was stirred for 2 hrs. at room temperature. On the other hand, 2-(2-nitrophenoxy)-2-phenoxyacetic acid (380 mg.), triethylamine (132 mg.) and N,N-dimethylbenzylamine (2 drops) were dissolved in methylene chloride (10 ml.), and the solution was cooled to −30°C. To the solution was added dropwise ethyl chloroformate (141 mg.), and the mixture was stirred for 40 minutes at the same temperature. To this solution was added all at once to a solution of 3-aminolactacillanic acid (320 mg.), N,O-stirred for 5.5 hrs. at −40 to −20°C. The solvent was distilled off from the reaction mixture under reduced pressure, and into the residue were poured ethyl acetate and a sodium bicarbonate aqueous solution. The aqueous layer separated out was adjusted to pH 1 to 2 with 10% hydrochloric acid, and then the mixture was extracted with ethyl acetate. The extract was washed with a sodium bicarbonate-saturated-aqueous solution and dried over anhydrous magnesium sulfate, and then the solvent was distilled off from the solution. The residue (540 mg.) obtained was dissolved in a small amount of acetone and sodium 2-ethylhexanate was added to the solution. To the solution was added ether, and the precipitating crystals were collected by filtration and washed with a mixed solvent of ether and acetone to give crystals of 3-[2-(2-nitrophenoxy)-2-phenoxyacetamido]lactacillanic acid sodium salt (380 mg.). Mp 169 to 172°C (dec.).

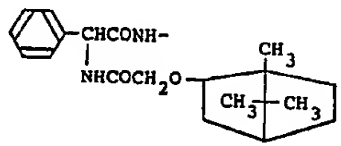
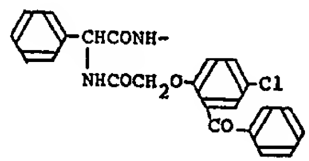
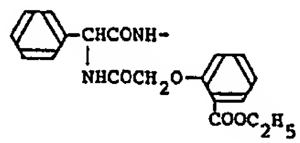
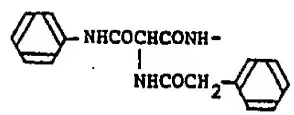
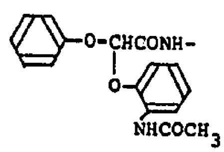
The following compounds were obtained in substantially the similar manner as described above.

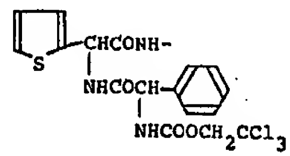
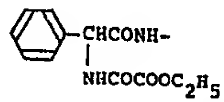
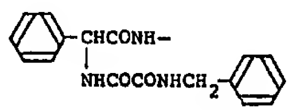
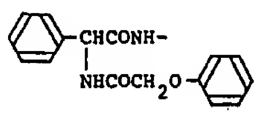
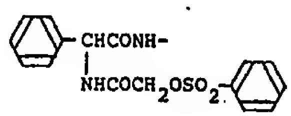
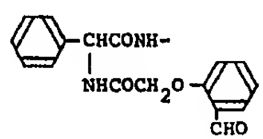


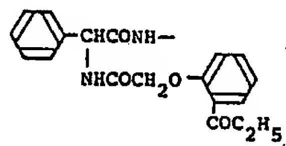
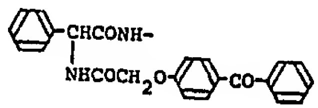
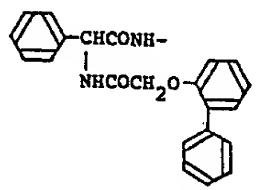
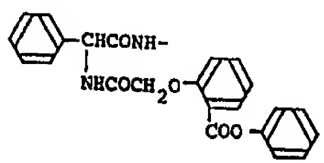
(I)

Example	R_1	A	mp(°C) (dec.)
151			143 - 146
152		"	115 - 118
153		"	130 - 135
154		"	111 - 116
155		"	(sodium salt) 221 - 224

156		"	160 - 164
157		"	112 - 116
158		"	122 - 124
159		"	77 - 81

160		"	130 - 134
161		"	135 - 137
162		"	127 - 130
163		"	(sodium salt) 183 - 188
164		"	(sodium salt) 192 - 197

165		"	165 - 169
166		"	118 - 123
167		"	149 - 154
168		"	107 - 111
169		"	151 - 155
170		"	191 - 195

171		"	125 - 130
172		"	154 - 159
173		"	125 - 130
174		"	143 - 148

Example 175.

2-[4-{3-(4-Nitrophenylthio)propoxy}phenyl]acetic acid (260 mg.) and thionyl chloride (300 mg.) were dissolved in chloroform (10 ml.), and the solution was heated for 2 hrs. under reflux. The chloroform and the excess of the thionyl chloride were distilled off from the reaction mixture under reduced pressure, and the residue obtained was dissolved in acetone (1 ml.). The acetone solution was added dropwise to a solution of 3-aminolactacillanic acid (180 mg.), sodium bicarbonate (160 mg.), water (5 ml.) and acetone (5 ml.) under cooling at 0 to 5°C, and then the reaction mixture was stirred for 45 minutes at the same temperature. The acetone was distilled off from the reaction mixture under reduced pressure, and into the residue obtained was poured ethyl acetate (40 ml.), and then the solution was adjusted to pH 1 with 10% hydrochloric acid. The ethyl acetate layer was separated out, and the remaining aqueous layer was extracted with ethyl acetate (20 ml.). The ethyl acetate layers were combined, washed with a sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. The solvent was distilled off from the solution to give crystals of 3-[2-[4-{3-(4-nitrophenylthio)propoxy}phenyl]acetamido]lactacillanic acid (400 mg.). Mp 142 to 146°C (dec.).

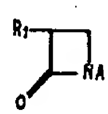
Example 176.

A dried tetrahydrofuran solution (10 ml.) containing 2-[2-(2-naphthoxy)acetamidooxy]-2-phenylacetic acid (351 mg.) and triethylamine (101 mg.) was cooled to −10°C, and to the solution was added dropwise a dried tetrahydrofuran solution (5 ml.) containing pivaloyl chloride (120 mg.), and the mixture was stirred for 1 hour at the same temperature. The solution was cooled to −30°C, and to the solution was added all at once a dried methylene chloride (5 ml.) containing 3-aminolactacillanic acid (236 mg.) and N,O-bis(trimethylsilyl)acetamide (600 mg.), and the reaction mixture was stirred for 1 hour at −10°C and for 1 hour at 0°C. The solvent was distilled off from the reaction mixture under reduced pressure, and into the residue was poured a sodium bicarbonate-saturated-aqueous solution. The aqueous solution was washed with ethyl acetate, adjusted to pH 1 to 2 with 10% hydrochloric acid and then extracted with ethyl acetate. The extract was washed with water and a sodium chloride-saturated-aqueous solution, respectively, and then dried over anhydrous magnesium sulfate. The solvent was distilled off from the solution, and the residue obtained was powdered with ether to give crystals of 3-[2-{2-(2-naphthoxy)acetamidooxy}-2-phenylacetamido]lactacillanic acid (340 mg.). Mp 109 to 112°C (dec.).

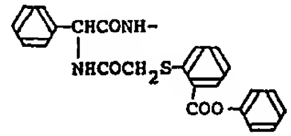
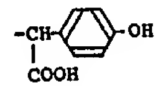
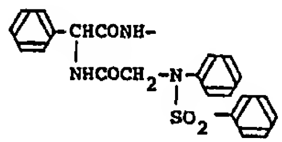
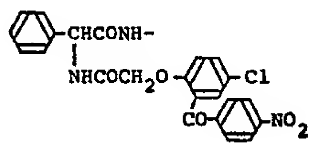
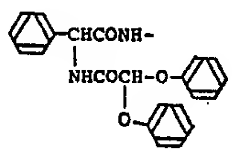
Example 177.

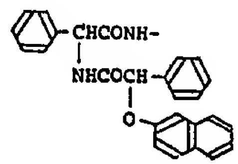
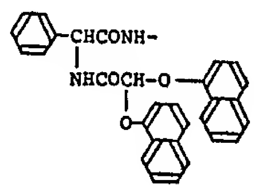
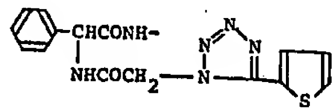
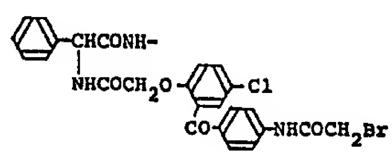
2-[2-Oxo-3-(2-phenylacetamido)-1-azetidinyl]-3-methylbutyric acid (455 mg.), triethylamine (151 mg.) and N,N-dimethylbenzylamine (2 drops) were added to methylene chloride (10 ml), and the solution was cooled to −30°C. The solution was added dropwise a methylene chloride (5 ml.) solution containing ethyl chloroformate (163 mg.). The solution was cooled to −40°C, and to the solution was added all at once a solution, prepared by dissolving 3-aminolactacillanic acid (389 mg.), N,O-bis-(trimethylsilyl)acetamide (1.0 g.) and N,N-dimethylformamide (0.25 ml.) in methylene chloride (10 ml.) and then by stirring the solution for 3 hrs. at room temperature. The reaction mixture was reacted for 1.5 hrs. under stirring. The solvent was distilled off from the reaction mixture, and to the residue were added ethyl acetate and a sodium bicarbonate aqueous solution, and then the aqueous layer was separated out. The aqueous layer obtained was adjusted to pH 1 to 2 with 1N-hydrochloric acid, and extraction was carried out by adding ethyl acetate to the solution. The ethyl acetate layer was separated out, and the remaining aqueous layer was also extracted with ethyl acetate. These ethyl acetate layers were combined, washed with a sodium chloride-saturated-aqueous solution and dried over anhydrous magnesium sulfate. The solvent was distilled off from the solution, and the powder (480 mg.) obtained was washed with ether to give crystals of 3 - [2 - {2 - oxo - 3 - (2 - phenylacetamido) - 1 - azetidinyl} - 3 - methylbutyramido]-lactacillanic acid (359 mg.). Mp 160 to 164°C (dec.).

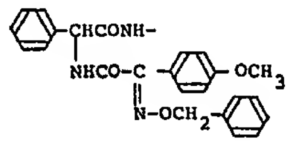
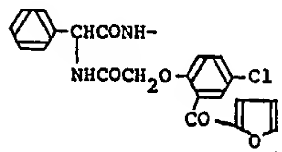
The following compounds were obtained in substantially the similar manner as described above.



(I)

Example	R_1	A	mp (°C) (dec.)
178			141 - 146
179		"	137 - 142
180		"	148 - 153
181		"	102 - 105

182		"	158 - 161
183		"	135 - 139
184		"	170 - 174
185		"	158 - 162

186		"	118 - 121
187		"	141 - 144

Example 188.

2-Methyl-5,6-dihydro-1,4-oxathiin-2-carboxylic acid (0.320 g.) was dissolved in chloroform (10 ml.). To the solution was added a dried methylene chloride solution (5 ml.) containing thionyl chloride (7 ml.), and the mixture was heated for 4 hrs. under reflux, and then concentrated to give a solution of an acid chloride of a 2-methyl-5,6-dihydro-1,4-oxathiin-3-carboxylic acid. On the other hand, 3-aminolactacillanic acid (0.236 g.) was suspended in dried methylene chloride (20 ml.), and N,O-bis-(trimethylsilyl)acetamide (1.50 g.) was added to the suspension, and then the mixture was stirred for 4 hrs. at ambient temperature. To the solution obtained was added dropwise the acid chloride solution prepared above under cooling to −5 to 0°C, and the mixture was stirred for 2 hrs. at the same temperature, and further stirred for 50 hrs. at ambient temperature. The reaction mixture was concentrated under reduced pressure to give a residue. Ethyl acetate and a sodium bicarbonate aqueous solution were poured into the residue and the mixture was stirred enough, whereafter the aqueous layer was separated out. The aqueous layer was washed with ether, and adjusted to pH 1 to 2 with diluted hydrochloric acid, and then the solution was extracted with ethyl acetate. The extract was washed with water, and dried over anhydrous magnesium sulfate. The solvent was distilled off from the solution to give a powder. Hot ethyl acetate (5 ml.) was added to the powder, and an insoluble material in the mixture was collected by filtration to give crude 3-(2-methyl-5,6-dihydro-1,4-oxathiin-3-carbonylamino)lactacillanic acid (240 mg.). This product was recrystallized from acetone to give the purified object compound (172 mg.). Mp 172.5 to 175.0°C (dec.).

Example 189.

3-Aminolactacillanic acid (0.708 g.) was suspended in dried methylene chloride (20 ml.). To the suspension was added N,O-bis(trimethylsilyl)acetamide (2.0 g.), and the mixture was stirred for a while to dissolve it. On the other hand, N-[4-(3-benzyloxycarbonyl-5-oxo-1,3-oxazolidin-4-yl)butyryl]succinimide (1.212 g.) was dissolved in dioxane (15 ml.), and the solution was cooled to 0 to 5°C. To the solution was added dropwise the solution obtained above, and the mixture was stirred for 6 hrs. at the same temperature. The reaction mixture was concentrated under reduced pressure to give a residue, and 5% sodium bicarbonate aqueous solution and ethyl acetate were added to the residue. The aqueous layer was separated out and washed with ethyl acetate twice. The aqueous solution was adjusted to pH 1 to 2 with diluted hydrochloric acid and then extracted with ethyl acetate. The extract was washed with water and dried over anhydrous magnesium sulfate. The solvent was distilled off from the solution, and the oily material (0.470 g.) obtained was subjected to column chromatography using silica: gel (10 g.). An elution was conducted with a mixture of ethyl acetate and methanol (volume ratio, 50:1), and the fractions containing the object compound were collected. These fractions were combined, and the solvent was distilled off from the solution to give 3-[4-(3-benzyloxycarbonyl-5-oxo-1,3-oxazolidin-4-yl)butyramido]-lactacillanic acid (0.100 g.).

I.R. absorption spectrum,

ν cm^{-1} (Nujol): 1730, 1720, 1700—1680, 1650.

Example 190.

3-Aminolactacillanic acid (472 mg.), 2-(2-propionylphenoxy)acetic acid (458 mg.), and ethyl chloroformate (238 mg.) was treated in substantially the similar manner as described in Example 109 to give 3-[2-(2-propionylphenoxy)acetamido]lactacillanic acid (40 mg.). Mp 114 to 118°C (dec.).

Example 191.

3-Aminolactacillanic acid (0.236 g.), 2-[4-{4-chloro-N-(2,2,2-trichloroethoxycarbonyl)anilinomethyl}phenoxy]-2-methylpropionic acid (0.610 g.) and thionyl chloride (7 ml.) were treated in substantially the similar manner as described in Example 120 to give 3-[2-[4-{4-chloro-N-(2,2,2-trichloroethoxycarbonyl)anilinomethyl}phenoxy]-2-methylpropionamido]lactacillanic acid (450 mg.). Mp 76 to 82°C (dec.).

Example 192.

1 - (1 - Methoxycarbonyl - 2 - methyl - 1 - propenyl) - 3 - phenoxyacetamido-2-azetidinone (1.0 g.) was dissolved in methylene chloride (40 ml.). To the solution was added N,N-dimethylaniline (0.55 g.), and the solution was cooled to −35 to −30°C. Phosphorus pentachloride (0.94 g.) was added to the solution all at once under stirring, and then the reaction mixture was stirred for 1.5 hrs. at the same temperature. Methanol (0.9 g.) was added to the reaction mixture, and then the solution was stirred for an hour at the same temperature. Elevating the reaction temperature to 0 to 5°C, water (0.6 ml.) was added to the solution, and the solution was stirred for an hour. The reaction mixture was extracted with water three times (total volume: 10 ml.), and these aqueous extracts were combined and adjusted to about pH 7 with sodium bicarbonate. The aqueous solution was washed with ethyl acetate (10 ml.) and ethyl acetate (5 ml.) respectively.

The aqueous layer was salted out with sodium chloride and then extracted with chloroform (8 ml.) seven times. These chloroform extracts were combined and dried over anhydrous magnesium sulfate, and the solvent was distilled off from the solution to give crystals of 3-amino-1-(1-methoxycarbonyl-2-methyl-1-propenyl)-2-azetidinone (0.34 g.). A part of this product was treated with p-toluen sulfonic acid in a conventional manner to give p-toluensulfonic acid salt of an object compound. Mp 169 to 171°C (dec.).

Example 193.

1 - (1 - Carboxy - 2 - methylpropyl) - 3 - phenylacetamido - 2 - azetidinone (1.52 g.) and N,N-dimethylaniline (2.15 g.) were suspended in methylene chloride (12 ml.), and to the suspension was added trimethylsilyl chloride (0.88 g.). The solution was stirred for 30 minutes at ambient temperature and cooled to −50°C. Phosphorus pentachloride (1.1 g.) was added to the solution and the solution was stirred for 2 hrs. (the reaction temperature was elevated to about −30°C during the stirring.). The solution was cooled to −50°C, and n-butyl alcohol (1.85 g.) was added to the solution, and then the solution was stirred for 2 hrs. (in this time, the reaction temperature was elevated to about −30°C). The solution was cooled again to −50°C, and a

solution preparing by dissolving sodium bicarbonate (1.3 g) in water (15 ml.), was added to the solution (in this time, the reaction temperature was elevated to about −25°C, and the solution indicated about pH 3). The solution was adjusted to pH 4 with sodium bicarbonate, and then the aqueous layer was separated out and washed with ether. The solution was evaporated to dryness under reduced pressure, keeping the temperature of the solution under 25°C. To the residue obtained was added isopropyl alcohol (15 ml.), and the mixture was filtered to obtain an insoluble material and a filtrate. The filtrate was evaporated to dryness under reduced pressure. This operation was repeated twice to give colorless powdery 3-amino-1-(1-carboxy-2-methylpropyl)-2-azetidinone (0.3 g.). These insoluble materials in isopropyl alcohol obtained above were combined and dissolved in a small amount of water, and the solution was adjusted to pH 2.5 with 1N-hydrochloric acid. The aqueous solution was evaporated to dryness under reduced pressure at 25°C, and the residue obtained was treated with isopropyl alcohol in the similar manner as described above to recover an object compound (0.13 g.). Total yield was 0.43 g. This product was treated in a conventional manner to give its salt of D-camphor-10-sulfonic acid, and the salt was recrystallized from a mixture of acetone and ether to give D-camphor-10-sulfonic acid salt of the object compound. Mp 178 to 183°C.

Example 194.

3 - [2 - {4 - (3 - Benzamido - 3 - carboxypropoxy)phenyl} - 2 - (3 - phenylthioureido)acetamido]lactacillanic acid (7.2 g.) was dissolved in acetic acid (20 ml.), and to the solution was added dropwise concentrated hydrochloric acid (2 ml.) under cooling while stirring. The reaction mixture was stirred for 1.5 hrs. and poured into a mixture of ice-water (50 ml.) and ethyl acetate (50 ml.).

The mixture was separated into a ethyl acetate layer and an aqueous layer. The ethyl acetate layer was extracted with ice-water (20 ml.). This aqueous layer and the aqueous layer obtained above were combined, and washed with ethyl acetate (20 ml.). To the aqueous layer was added a weak basic anion-exchange resin, Amberlite IR—45 (OH type) (trade mark, maker: Rohm and Haas Co. Ltd.,) (60 ml.), and the mixture was stirred under ice-cooling, and then filtered. The resin was washed with ice-water (10 ml.), and then the washing and the filtrate were combined, and concentrated under reduced pressure to obtain a residue. Methanol was added to the residue, and then the residue was collected by filtration. The residue was washed with acetone to give 3-aminolactacillanic acid. (0.59 g.). Mp 203 to 206°C (dec.).

I.R. absorption spectrum,
ν cm^{-1} (Nujol): 1763, 1742

N.M.R. absorption spectrum,
δ_{ppm} (D_2O+NaOD): 2.89 (1H, d,d, J=3H, 6Hz)
3.79 (1H, t, J=6Hz)
4.22 (1H, d,d, J=3Hz, 6Hz)
5.26 (1H, s)
6.91 (2H, d, J=9Hz)
7.23 (2H, d, J=9Hz)

Example 195.

3-(2-Phenylacetamido)lactacillanic acid was treated in substantially the similar manner as described in Example 193 to give 3-amino-lactacillanic acid, which was identified by comparing an I.R. absorption spectrum, a N.M.R. absorption spectrum and a melting point with an authentic sample.

Example 196.

3 - [2 - [4 - {3 - (3 - Phenylthioureido) - 3 - carboxypropoxy}phenyl] - 2 - (3-phenylthioureido)acetamido]lactacillanic acid (1.44 g.) was suspended in water (10 ml.), and to the suspension was added anhydrous potassium carbonate (0.56 g.). The solution (pH 9) was stirred for 27 hrs. at 30°C, and then was filtered. The filtrate was diluted by adding ethanol (50 ml.) and the solution was allowed to stand under ice-cooling to give a precipitate. The precipitate was filtered off, and the filtrate was concentrated under reduced pressure to give a residue. The residue was adjusted to pH 2 with 5% hydrochloric acid, and then washed with ethyl acetate. The solution was adjusted to pH 7.5 with sodium carbonate, and then evaporated to dryness under reduced pressure to obtain the powder (0.75 g.). Water (7 ml) was added to the powder, and an insoluble material in the water was collected by filtration and washed with water to give 3-aminolactacillanic acid (40 mg.). The filtrate and the washing were combined, and the combined solution was treated with an activated carbon to give crude crystals of 3-aminolactacillanic acid (123 mg.). These object compounds were

combined and suspended in 30% aqueous methanol solution. The suspension was stirred for an hour, and, then filtered to give the purified crystals of 3-aminolactacillanic acid (133 mg.), which was identified by comparing an I.R. absorption spectrum, a N.M.R. absorption spectrum and a melting point with an authentic sample.

Example 197.

3 - [2 - [4 - {3 - (3 - Phenylthioureido) - 3 - carboxypropoxy}phenyl] - 2 - (3-phenylthioureido)acetamido]lactacillanic acid (0.36 g.) was dissolved in methanol (3 ml.), and concentrated hydrochloric acid (0.1 ml.) was added to the solution under ice-cooling, and then the reaction mixture was stirred for 30 minutes. Sodium bicarbonate (0.08 g.) was added to the reaction mixture, and the solution was stirred for 10 minutes. Ice-water (10 ml.) was poured into the solution, and the solution was filtered to remove precipitating crystals. The filtrate was washed with ethyl acetate (10 ml.) and evaporated to dryness under reduced pressure. Methanol was added to the residue to give crystals and the crystals were collected by filtration to give 3-amino-lactacillanic acid (10 mg.). The mother liquor was concentrated to recover an object compound (80 mg.), which was identified by comparing an I.R. absorption spectrum, a N.M.R. absorption spectrum, and a melting point with an authentic sample.

Example 198.

3 - [2 - [4 - {3 - (3 - Phenylthioureido) - 3 - carboxypropoxy}phenyl] - 2 - (3-phenylthioureido)acetamido]lactacillanic acid (0.50 g.) was dissolved in 2,2,2-trifluoroacetic acid (4 ml.), and the solution was stirred for an hour under ice-cooling. The reaction mixture was poured into ice-water (about 10 ml.), and the solution was washed with ethyl acetate (10 ml.) twice. The aqueous solution was adjusted to pH 4 with a weak basic anion-exchange resin, Amberlite IR—45 (OH type) (trade mark, maker; Rohm and Haas Co. Ltd.,) (9.5 ml.), and the resin was filtered off from the mixture, and then the filtrate was concentrated to give residues. Methanol was added to the residues to give crystals, which were collected by filtration to give 3-amino-lactacillanic acid (30 mg.). This product was identified by comparing an I.R. absorption spectrum, a N.M.R. absorption spectrum, and a melting point with an authentic sample.

Example 199.

3 - [2 - {4 - (3 - Acetamido - 3 - carboxypropoxy)phenyl} - 2 - (3 - phenylthioureido)acetamido]lactacillanic acid (0.67 g.) was dissolved in acetic acid (6.7 ml.), and to the solution was added all at once concentrated hydrochloric acid (0.15 ml.) under water-cooling while stirring, and then the reaction mixture was stirred for an hour. The reaction mixture was treated in substantially the similar manner as described in Example 198 to give 3-aminolactacillanic acid (90 mg.), which was identified by comparing an I.R. absorption spectrum and a N.M.R. absorption spectrum with an authentic sample.

Example 200.

3 - [2 - [4 - [3 - Carboxy - 3 - {N - ethoxy(thiocarbonyl)aminopropoxy}]-phenyl] - 2 - {N - ethoxy(thiocarbonyl)amino}acetamido]lactacillanic acid was treated in substantially the similar manner as described in Example 199 to give 3-aminolactacillanic acid.

Example 201.

3 - [2 - [4 - {3 - (3 - Phenylthioureido) - 3 - carboxypropoxy}phenyl] - 2 - (3-phenylthioureido)acetamido]lactacillanic acid (2.28 g.) was dissolved in acetic acid (6 ml.), and to the solution was added dropwise a mixture of concentrated hydrochloric acid (0.45 ml.) and acetic acid (6 ml.) during 15 minutes under water-cooling while stirring. Furthermore, the reaction mixture was stirred for 15 minutes, and ethyl acetate (25 ml.) and water (25 ml.) were added to the reaction mixture, whereafter the mixture was stirred. The ethyl acetate layer separated out was extracted with water (10 ml.). This extract and the aqueous layer obtained above were combined, and the combined aqueous solution was washed with ethyl acetate and adjusted to pH 3.4 with a weak basic anion-exchange resin, Amberlite I.R.—45 (OH type) (trade mark, maker: Rohm and Haas Co. Ltd.) (15 ml.). The resin was filtered off from the mixture, and the filtrate was concentrated under reduced pressure to give residues. Methanol was added to the residues to give crystals, which were collected by filtration to give 3-amino-lactacillanic acid (0.25 g.). This product was identified by comparing an I.R. absorption spectrum, a N.M.R. absorption spectrum, and a melting point with an authentic sample.

Example 202.

3 - [2 - {4 - (3 - Benamido - 3 - carboxypropoxy)phenyl} - 2 - (2 - nitro - 4-methoxycarbonylanilino)acetamido]lactacillanic acid (1.54 g.) was dissolved in a mixture of water (10 ml.) and methanol (20 ml.), and to the solution was added 10% palladium : carbon (500 mg.) as a catalyst. The solution was stirred for 2 hrs. in hydrogen atmosphere under increased pressure using a middle-pressure reduction apparatus at ambient temperature. After the reaction was completed, the catalyst was filtered off, and the methanol was distilled off from the filtrate under reduced pressure. The remaining solution was washed with ethyl acetate and cooled. Acetone was added to the solution to give precipitating crystals, which were collected by filtration to give 3-aminolactacillanic acid (83 mg.). Furthermore, the mother liquor was evaporated to dryness under reduced pressure, and the residue obtained was washed with methanol to give crystals. The crystals were collected by filtration to give an object compound (50 mg.). Total yield was 123 mg. This product was identified by comparing an I.R. absorption spectrum and a N.M.R. absorption spectrum with an authentic sample.

Example 203.

3 - [2 - [4 - {3 - (2 - Nitro - 4 - methoxycarbonylanilino) - 3 - carboxypropoxy}-phenyl] - 2 - (2 - nitro - 4 - methoxycarbonylanilino)acetamido]lactacillanic acid was treated in substantially the similar manner as described in Example 202 to give 3-aminolactacillanic acid.

Example 204.

3 - [2 - {4 - (3 - Acetamido - 3 - carboxypropoxy)phenyl} - 2 - {3 - (1 - naphthyl)thioureido}acetamido]lactacillanic acid (2.5 g.) was dissolved in acetic acid (10 ml.), and to the solution was added concentrated hydrochloric acid (0.56 ml.) under water-cooling while stirring. The reaction mixture was stirred for 30 minutes, and then poured into a mixture of ice-water (10 ml.) and ethyl acetate (20 ml.), and the aqueous layer was separated out. The remaining ethyl acetate layer was extracted with ice-water (10 ml.). The aqueous layers were combined and washed with ethyl acetate (10 ml.). A weak basic anion-exchange resin, Amberlite IR—45 (OH type) (trade mark, maker; Rohm and Haas Co., Ltd.) (15 ml.) was added to the solution, and then the mixture (pH 3.4) was stirred for 5 minutes. The resin was filtered off from the mixture and washed with ice-water (5 ml.). The filtrate and the washing were combined and concentrated to give residues. The residues were washed with methanol to give crystals. The crystals were collected by filtration to give 3-aminolactacillanic acid (149 mg.). Furthermore, the mother liquor was concentrated, and the residue obtained was washed with methanol to recover an object compound (80 mg.). Total yield was 229 mg. This product was identified by comparing an I.R. absorption spectrum and a N.M.R. absorption spectrum with an authentic sample.

Example 205.

3 - [2 - [4 - [3 - Carboxy - 3 - {3 - (1 - naphthyl)thioureido}propoxy]phenyl]-2 - {3 - (1 - naphthyl)thioureido}acetamido]lactacillanic acid (2.6 g.) was reacted in substantially the similar manner as described in Example 204 to give 3-aminolactacillanic acid (190 mg.), which was identified by comparing an I.R. absorption spectrum and a melting point with an authentic sample.

Example 206.

3-(2-Phenylacetamido)-2-azetidinone (816 mg.) and benzyl 2-bromo-2-phenylacetate (1.22 g.) were dissolved in N,N-dimethylformamide (20 ml.), and to the solution was added sodium hydride (50% oily) (210 mg.) in nitrogen atmosphere under ice-cooling while stirring, and then the reaction mixture was stirred for an hour at the same temperature. Ethyl acetate (150 ml.) was added to the reaction mixture, and the solution was washed with water, a sodium bicarbonate-saturated-aqueous solution and water respectively, and the dried over anhydrous magnesium sulfate. The solution was evaporated to dryness under reduced pressure to give the yellow oily material (1.7 g.). The material was subjected to column chromatography using silica : gel (developer: chloroform to give two isomers of 1-(α-benzyloxycarbonylbenzyl)-3-(2-phenyl)acetamido-2-azetidinone. Yield of the isomer A is 26 mg. and it of the isomer B is 65 mg.

Physical constant of isomer A:

Oil

Mass spectrum,

m/e=428 (M^+)

I.R. absorption spectrum,

ν cm^{-1} ($CHCl_3$): 1760, 1740 (shoulder), 1678.

N.M.R. absorption spectrum,

δ_{ppm} ($CDCl_3$): 3.46 (2H, m), 3.55 (2H, s), 4.96 (1H, m), 5.15 (2H, s), 5.61 (1H, s), 6.37 (1H, d, J=8Hz), 6.90—7.60 (15H, m).

Physical constant of isomer B:

Mp: 96 to 98°C

Mass spectrum,

m/e=428 (M^+)

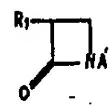
I.R. absorption spectrum,

ν cm^{-1} (Nujol): 1750, 1732, 1680.

N.M.R. absorption spectrum:

δ_{ppm} ($CDCl_3$): 3.03 (1H, d,d, J=3Hz, 5Hz), 3.53 (2H, s), 3.85 (1H, d,d, J=5Hz, 5 Hz), 4.88 (1H, m), 5.17 (2H,s), 5.62 (1H,s), 6.05 (1H,d, J=8Hz), 7.00—7.60 (15H, m).

The following compounds were obtained in substantially the similar manner as described above.



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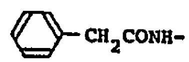
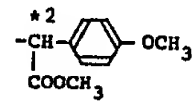
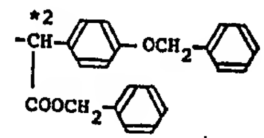
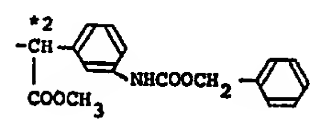
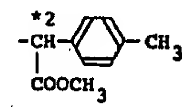
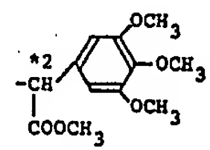
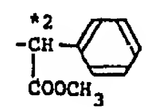
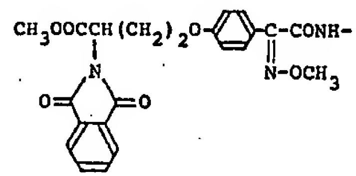
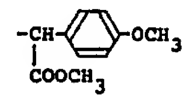
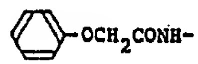
Example	R_1	A'	mp (°C) (dec.) (Note 2)
207			(D isomer) 145 - 146 (L isomer) I.R. ν cm^{-1} ($CHCl_3$): 1760, 1740, 1680
208	"		(D isomer) 129 - 130 (L isomer) I.R. ν cm^{-1} (liquid film): 1760 - 1740, 1665
209	"		isomer A) N.M.R. δ ppm ($CDCl_3$): 3.5(2H,m), 3.6(2H,s), 3.7(3H,s), 5.0(1H,m), 5.2(2H,s), 5.5(1H,s), 6.3(1H,d,J=8Hz), 6.9-7.6(15H,m) isomer B) N.M.R. δ ppm ($CDCl_3$): 3.0(1H,d,d,J=3Hz,6Hz), 3.4(2H,s), 3.7(3H,s), 3.8(1H,d,d,J=3Hz,6Hz), 4.9(1H,m), 5.2(2H,s), 5.6(1H,s), 6.5(1H,d,J=8Hz), 6.9-7.6(15H,m)

210	"		isomer A) 148 isomer B) I.R. ν cm^{-1} (Nujol): 1755, 1745, 1675
211	"		isomer A) 138 - 140 isomer B) N.M.R. δ ppm ($CDCl_3$): 3.54(2H,m), 3.59(2H,s), 3.73 (3H,s), 3.82(9H,s), 4.96(1H, m), 5.45(1H,s), 6.13(1H,d, J=8Hz), 6.43(2H,s), 7.10-7.45 (5H,m)
212	"	$-CH_2COOC_2H_5$	104 - 105
213	"		114 - 115
214	"		isomer A) 138 - 140 isomer B) I.R. ν cm^{-1} ($CHCl_3$): 1770, 1745, 1678

215			I.R. ν cm^{-1} (liquid film): 1745, 1720. 1675
216		"	I.R. ν cm^{-1} (NaCl): 1770, 1740, 1680

Note 1. The compound marked by *1 is D isomer at the asymmetric carbon marked by *1.
2. a) D or L Isomer is one at the asymmetric carbon marked by *2.
b) Isomer A or B is one at the asymmetric carbon marked by *2.

Example 217.

3-(2-Phenylacetamido)-2-azetidinone (610 mg.), methyl 2-bromo-2-(3-nitrophenyl)acetate (900 mg.) and anhydrous potassium carbonate (460 mg.) were added to ethyl methyl ketone (60 ml.), and the solution was heated for 8 hrs. under reflux while stirring. The reaction mixture was cooled and then poured into ice-water, whereafter the mixture was extracted with ethyl acetate. The extract was washed with a sodium chloride-saturated-aqueous solution, and then dried over anhydrous magnesium sulfate. The solution was evaporated to dryness, and the oily residue obtained was subjected to column chromatography. The fractions, eluted with a mixture of chloroform and methanol (100:1), was subjected to thin layer chromatography using silica : gel [developer: a mixed solvent of chloroform and methanol (40:1)] to give a mixture of two isomers of 1-(α-methoxycarbonyl-3-nitrobenzyl)-3-(2-phenylacetamido)-2-azetidinone (7.5 mg.).

I.R. absorption spectrum:

ν cm^{-1} ($CHCl_3$): 1765, 1745, 1680.

Example 218.

3-(2-Phenylacetamido)-2-azetidinone (612 mg.) and methyl 2-bromo-2-(4-methylthiophenyl)acetate (825 mg.) were dissolved in N,N-dimethylformamide (20 ml). Keeping a temperature of the solution at 20 to 30°C, a benzene (20 ml.) solution of sodium N,N-bis(trimethylsilyl)amine (546 mg.) was added to the solution during an hour in nitrogen atmosphere, and the reaction mixture was stirred for 15 minutes at

the same temperature. Ethyl acetate (150 ml.) was added to the reaction mixture, and the ethyl acetate layer was washed with water, a sodium bicarbonate-saturated-aqueous solution and water respectively, and then dried over anhydrous magnesium sulfate. The solvent was distilled off from the solution to give the oily residue (1.2 g). The residue was subjected to column chromatography using silica : gel (developer: chloroform) to give two isomers of 1-(α-methoxycarbonyl-4-methylthiobenzyl)-3-phenylacetamido-2-azetidinone. Yield of the isomer A: 10 mg, mp 115 to 117°C (dec.): Yield of the isomer B: 43.5 mg, mp 157 to 159°C (dec.).

Example 219.

3-(2-Phenylacetamido)-2-azetidinone (408 mg.) and 2-chloroacetonitrile (152 mg.) was dissolved in N,N-dimethylformamide (15 ml.), and to the solution was added sodium hydride (50% oily) (105 mg.) under stirring at ambient temperature, whereafter the reaction mixture was stirred for an hour at room temperature, and ethyl acetate (100 ml.) was added to the reaction mixture. The ethyl acetate layer was washed with water and dried over anhydrous magnesium sulfate, and then the solvent was distilled off from the solution under reduced pressure. The oily residue (0.25 g.) obtained was subjected to column chromatography using silica : gel. 1-Cyanomethyl-3-(2-phenylacetamido)-2-azetidinone (56.3 mg.) was obtained from fractions eluted with chloroform. Mp 108 to 109°C (dec.).

Example 220.

2-(2-Phenoxyacetamido)-2-azetidinone (154 mg.) was dissolved in N,N-dimethylformamide (1.75 ml.), and to the solution was added all at once thallium ethoxide (174.6 mg.), and then the mixture was stirred for 10 minutes at ambient temperature. To the reaction mixture was added dropwise a solution, prepared by dissolving ethyl 2-bromo-2-(4-ethoxycarbonyloxyphenyl)acetate (232 mg.) in N,N-dimethylformamide (0.6 ml.), was added to the reaction mixture and then the reaction mixture was stirred for 2 hrs. at ambient temperature. The reaction mixture was filtered to give insoluble materials and a filtrate. The insoluble materials were washed with ethyl acetate. The filtrate and the washing were combined and diluted with ethyl acetate. The solution was washed with water and dried over anhydrous magnesium sulfate. The solution was concentrated under reduced pressure to give the yellow oily residue, which was subjected to column chromatography using silica gel. Oil of 1-(α-ethoxycarbonyl-4-ethoxycarbonyloxybenzyl)-3-(2-phenoxyacetamido)-2-azetidinone was obtained from fractions eluted with benzene.

I.R. absorption spectrum;

ν cm^{-1} (liquid film): 1760, 1740 (shoulder), 1675.

Example 221.

A isomer B of 1-(α-benzyloxycarbonylbenzyl)-3-(2-phenylacetamido)-2-azetidinone (63 mg.) obtained in Example 206 was dissolved in isopropyl alcohol (12 ml.), and to the solution was added 10% palladium : carbon (10 mg.). The mixture was reacted in hydrogen atmosphere at ordinary temperature and ordinary atm. until the absorption of hydrogen gas was completed. The catalyst was filtered off, and the solvent was distilled off from the filtrate, and then ether was added to the residue obtained to give crystals of 1-(α-carboxybenzyl)-3-(2-phenyl-acetamido)-2-azetidinone (27 mg.), which was recrystallized from a mixture of methanol and ether to give the purified object compound. Mp 174 to 175°C (dec.).

Example 222.

1-Carboxymethyl-3-(2-phenylacetamido)-2-azetidinone was obtained by treating 1-Benzyloxycarbonylmethyl-3-(2-phenylacetamido)-2-azetidinone in substantially the similar manner as described in Example 221. Mp 144 to 145°C.

Example 223.

3-(2-Phenylacetamido)-2-azetidinone (750 mg.) and benzyl 2-bromo-2-(4-benzyloxyphenyl)acetate (1.51 g.) was added to anhydrous N,N-dimethylformamide (10 ml.), and dissolved in it by warming for a while. The solution was cooled in an ice-water bath, and to the solution was added all at once sodium hydride (50% oily) (178 mg.) under stirring. After removing the cooling bath, the reaction mixture was stirred for 30 minutes to which ethyl acetate was added. The reaction mixture was filtered and the filtrate was washed with water, 2% hydrochloric acid and water respectively, and then dried over anhydrous magnesium sulfate. The solution was concentrated under reduced pressure to give an oily material (1.98 g.), which was subjected to column chromatography using silica : gel (40 g.). The fractions, eluted with a mixture of

benzene and chloroform were subjected to thin layer chromatography using silica : gel, and the thin layer was developed with a mixture of chloroform and acetone to give two isomers of 1-(α-benzyloxycarbonyl-4-benzyloxybenzyl)-3-(2-phenylacetamido)-2-azetidinone. The isomer A was recrystallized from a mixture of chloroform and ether. Yield: 90 mg. Mp: 129 to 130°C (dec.). The isomer B is oily material Yield: 120 mg. The isomer A (90 mg.) obtained above was dissolved in methanol (7 ml.), and to the solution was added 10% palladium carbon (30 mg.). The mixture was reacted in hydrogen atmosphere at ordinary temperature and ordinary atm. until the absorption of hydrogen gas was completed. The catalyst was filtered off from the reaction mixture, and the filtrate was concentrated under reduced pressure. The residue obtained was crystallized from a mixture of ethyl acetate and ether to give crystals of 3-(2-phenylacetamido)lactacillanic acid. The product was identified by comparing an I.R. absorption spectrum and a N.M.R. absorption spectrum and a melting point with an authentic sample synthesized by another method from 3-aminolactacillanic acid.

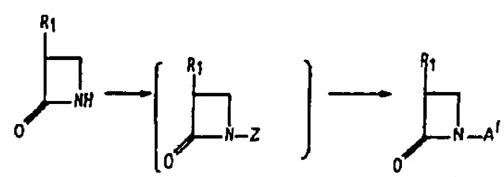
Example 224.

3-(2-Phenylacetamido)-2-azetidinone (300 mg.) and benzyl 2-bromo-2-(4-benzyloxyphenyl)acetate (604 mg.) were dissolved in anhydrous N,N-dimethylformamide (4 ml.) under warming. The solution was cooled in a cooling bath, to which was added all at once sodium hydride (50% oily) (71 mg.), and then the reaction mixture was stirred for a while. After removing the cooling bath, the reaction mixture was stirred for 30 minutes, whereafter ethyl acetate was added thereto. The reaction mixture was filtered and then the filtrate was washed with water, 2% hydrochloric acid and water respectively, and then dried over anhydrous magnesium sulfate. The solution was concentrated to give a oily residue (727 mg.), which was subjected to column chromatography using silica : gel (15 g.). Elution was carried out with a mixture of benzene and chloroform to obtain an oily material (255 mg.). A part of this material (20 mg.) was dissolved in methanol (14 ml.), and to the solution was added 10% palladium : carbon (60 mg.). The mixture was reacted in hydrogen atmosphere at ordinary temperature and ordinary atm. until the absorption of hydrogen gas was completed. The catalyst was filtered off from the reaction mixture, and the filtrate was concentrated under reduced pressure. The residue obtained was crystallized from a mixture of ethyl acetate and ether to give 3-(2-phenylacetamido)lactacillanic acid.

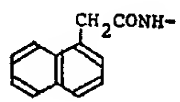
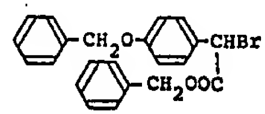
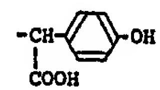
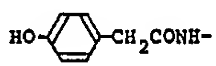
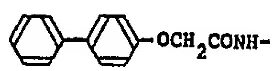
I.R. absorption spectrum,

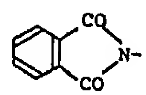
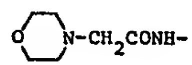
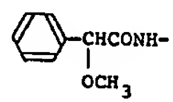
ν cm^{-1} (Nujol): 1745, 1690, 1650.

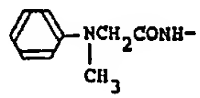
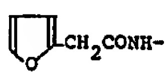
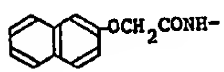
The folowing compounds were obtained in substantially the similar manner as described above.



(III) (I^{B})

Example	Compound (III) R_1	Reagent	Compound (I") R_1	Compound (I") A'	Compound (I") mp(°C) (dec.)
225			the same as R_1 of Compound (III)		I.R. $\nu_{cm^{-1}}$ (Nujol): 1740, 1690, 1660
226		"	"	"	I.R. $\nu_{cm^{-1}}$ (Nujol): 1740, 1650
227	$CH_3CH_2CH_2CONH$-	"	"	"	172 - 177
228	CH_3OCH_2CONH-	"	"	"	121 - 127
229		"	"	"	189 - 194

230		"	"	"	158 - 162
231	$(CH_3)_3CCONH-$	"	"	"	I.R. ν cm^{-1} (Nujol): 1745, 1680, 1640
232		"	"	"	191 - 196
233		"	"	"	192 - 198
234		"	"	"	I.R. ν cm^{-1} (Nujol): 1740, 1695, 1660
235	$HOOCCH_2CH_2CONH-$	"	"	"	(disodium salt) I.R. ν cm^{-1} (KBr): 1740, 1660, 1585

236		"	"	"	185 - 192
237		"	"	"	164 - 170
238		"	"	"	138 - 142

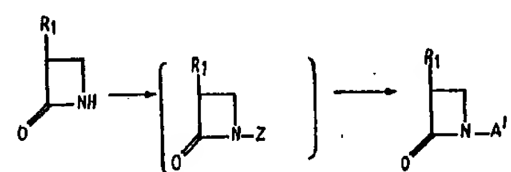
Example 239.

A crude product (157 mg.) without separation and purification thereof, obtained by the reacting 3-(2-phenoxyacetamido)-2-azetidinone and ethyl 2-bromo-2-(4-ethoxycarbonyloxyphenyl)acetate in the same manner as described in Example 220 similarly, was dissolved in ethanol (3 ml.). 1N Sodium hydroxide aqueous solution (1.0 ml.) was added to the solution under cooling in ice-water bath and then the solution was stirred for 30 minutes after removing the cooling bath. The reaction mixture was concentrated under reduced pressure, and water was added to the residue obtained. The aqueous solution was washed with ethyl acetate and then the aqueous layer was adjusted to pH 1 to 2 with 1N hydrochloric acid, whereafter was extracted with ethyl acetate. The extract was washed with a sodium chloride-saturated-aqueous solution, and dried over anhydrous magnesium sulfate. The solvent was distilled off from the solution under reduced pressure to give residues, which were washed with ether to give 3-(2-phenoxyacetamido)lactacillanic acid.

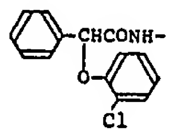
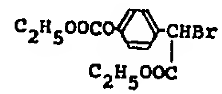
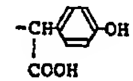
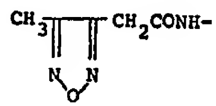
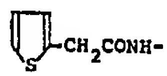
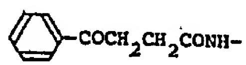
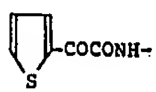
I.R. absorption spectrum;

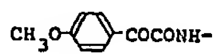
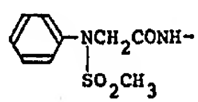
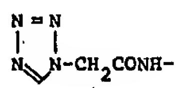
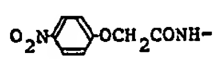
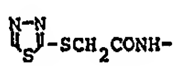
ν cm^{-1} (Nujol): 1745, 1690, 1660.

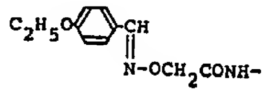
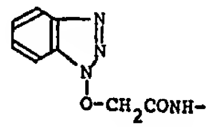
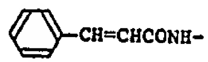
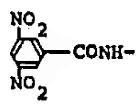
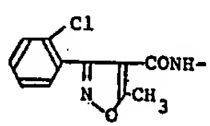
The corresponding 3-acylamino-2-azetidinone was treated in substantially the similar manner as described above, and the following compounds were obtained.

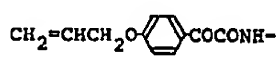
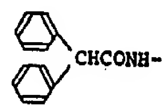
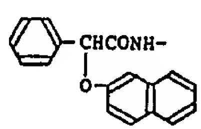
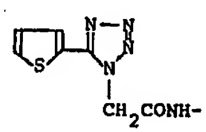
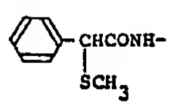


(III) (I'')

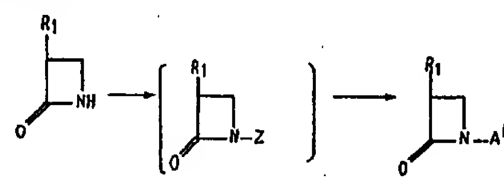
Example	Compound (III) R_1	Reagent	Compound (I") R_1	Compound (I") A'	Compound (I") mp(°C) (dec.)
240			the same as R_1 of Compound (III)		(sodium salt) I.R. ν cm^{-1} (Nujol): 1730, 1660, 1635, 1600
241		"	"	"	I.R. ν cm^{-1} (Nujol): 1740, 1680, 1665
242		"	"	"	I.R. ν cm^{-1} (Nujol): 1750, 1680, 1670
243		"	"	"	151 - 157
244		"	"	"	I.R. ν cm^{-1} (Nujol): 1745, 1690, 1640
245	$CH_3COCONH$-	"	"	"	155 - 161

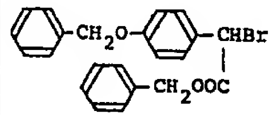
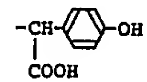
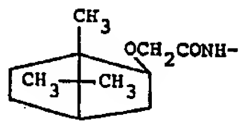
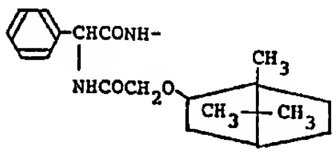
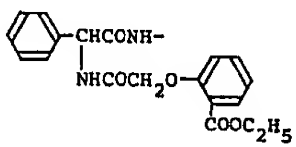
246		"	"	"	I.R. ν cm^{-1} (Nujol): 1745, 1695, 1660
247		"	"	"	112 - 117
248		"	"	"	170 - 175
249	$CH_2=CHCH_2SCH_2CONH-$	"	"	"	I.R. ν cm^{-1} (Nujol): 1745, 1680, 1660
250	CH_3SCH_2CONH-	"	"	"	146 - 151
251		"	"	"	I.R. ν cm^{-1} (Nujol): 1745, 1660
252		"	"	"	I.R. ν cm^{-1} (Nujol): 1745, 1685, 1660

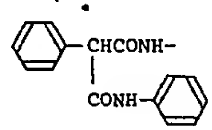
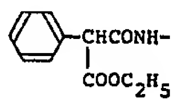
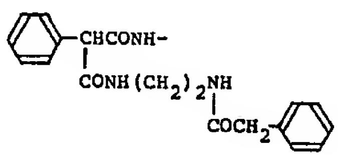
253		"	"	"	127 - 133
254		"	"	"	172 - 177
255		"	"	"	I.R. ν cm^{-1} (Nujol): 1740, 1680, 1655
256		"	"	"	I.R. ν cm^{-1} (Nujol): 1740, 1725 (s) 1690, 1665
257		"	"	"	190 - 195
258		"	"	"	(sodium salt) I.R. ν cm^{-1} (Nujol): 1735, 1655, 1610

259		"	"	"	I.R. ν cm^{-1} (Nujol): 1735, 1710, 1660
260		"	"	"	128 - 135
261		"	"	"	I.R. ν cm^{-1} (Nujol): 1740, 1690, 1670
262		"	"	"	191 - 195
263		"	"	"	I.R. ν cm^{-1} (Nujol): 1740, 1690, 1670, 1640

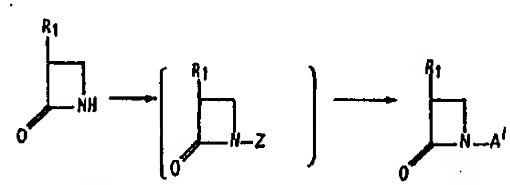
The 3-acylamino-2-azetidinone (III) shown in the following table was treated in substantially the similar manner as described in Example 224 to give the compound (I″) shown in the following table.

(III)  (I″)

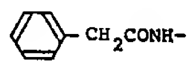
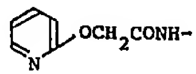
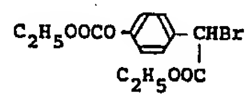
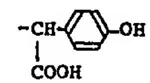
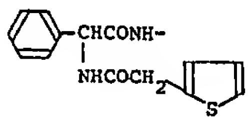
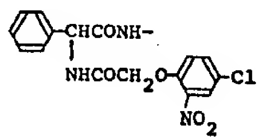
Example	Compound (III) R_1	Reagent	Compound (I") R_1	Compound (I") A'	Compound (I") mp(°C) (dec.)
264	$CH_3(CH_2)_{14}CONH-$		the same as R_1 of Compound (III)		157 - 161
265		"	"	"	106 - 109
266		"	"	"	130 - 134
267		"	"	"	127 - 130

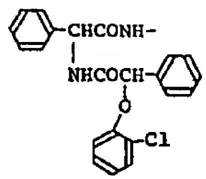
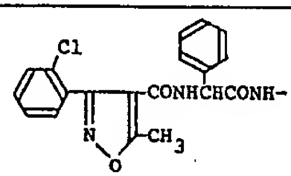
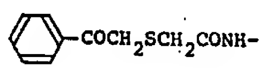
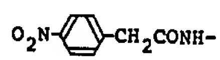
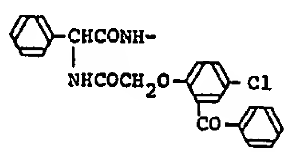
268		"	"	"	(sodium salt) 183 - 187
269		"	"	"	103 - 107
270		"	"	"	115 - 118

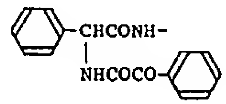
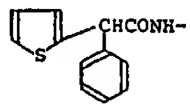
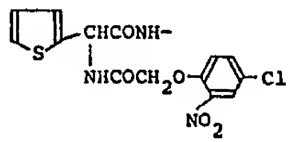
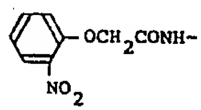
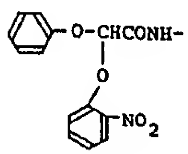
The 3-acylamino-2-azetidinone (III) shown in the following table was treated in substantially the similar manner as described in Example 239 to give the compound (I″) shown in the following table.

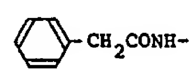
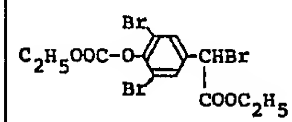
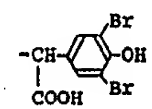
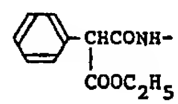
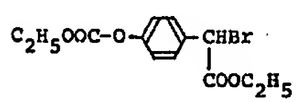
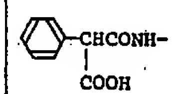
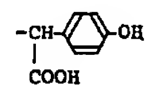


(III) (I″)

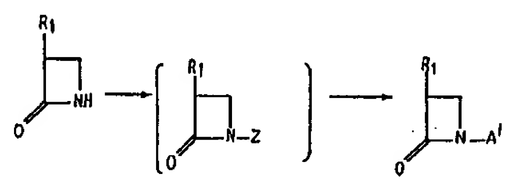
Example	Compound (III) R_1	Reagent	Compound (I") R_1	Compound (I") A'	Compound (I") mp(°C) (dec.)
271		$(CH_3)_2CHCH(Br)COOC_2H_5$	the same as R_1 of Compound (III)	$-CH(COOH)CH(CH_3)_2$	106 - 109
272			"		192.5 - 193
273		"	"	"	(sodium salt) 221 - 224
274		"	"	"	77 - 81

275		"	"	"	112 - 116
276		"	"	"	122 - 124
277		"	"	"	130 - 135
278		"	"	"	234 - 236
279		"	"	"	135 - 137

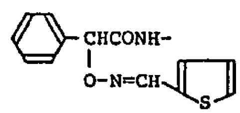
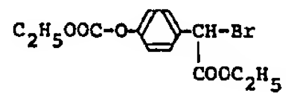
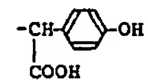
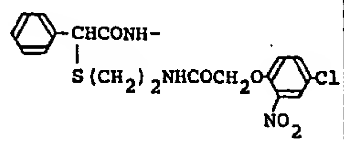
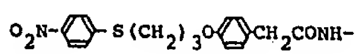
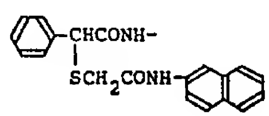
280		"	"	"	143 - 146
281		•	"	"	139 - 143
282		"	"	"	(sodium salt) 187 - 190
283		"	"	"	(sodium salt) 116
284		"	"	"	(sodium salt) 169 - 172

285			"		161 - 162
286					(disodium salt) 209 - 214

The 3-acylamino-2-azetidinone (III) was treated in substantially the similar manner as described in Example 239 to give the compound (I″) shown in the following table.



(III) (I″)

Example	Compound (III) R_1	Reagent	Compound (I") R_1	A'	mp(°C) (dec.)
287			the same as R_1 of Compound(III)		(sodium salt) I.R. ν cm^{-1} (Nujol): 1730, 1650, 1600
288		"	"	"	77 - 81
289		"	"	"	142 - 146
290		"	"	"	124 - 128

Example 291.

3 - [2 - {4 - (3 - Amino - 3 - carboxypropoxy)phenyl} - 2 - hydroxyiminoacetamido]lactacillanic acid (1.0 g.) was dissolved in 1.5% sodium bicarbonate aqueous solution (20 ml.), and to the solution was added sodium hydrogen sulfite (1.0 g.), and then the mixture was heated for 3 hrs. at 80°C. The reaction mixture was adjusted to pH 3 with 10% hydrochloric acid, and the mixture was concentrated to a volume of about 10 ml. and the concentrate was adjusted to pH 3 with 10% hydrochloric acid again to give crystals of 3-[4-(3-amino-3-carboxypropoxy)phenylglyoxyloylamino]-lactacillanic acid (0.57 g.). Mp 216°C (dec.).

Example 292.

3 - [2 - {4 - (3 - Acetamido - 3 - carboxypropoxy)phenyl} - 2 - hydroxyiminoacetamido]lactacillanic acid was treated in substantially the similar manner as described in Example 291 to give crystals of 3-[4-(3-acetamido-3-carboxypropoxy)phenylglyoxyloylamino]lactacillanic acid. Mp 96 to 102°C (dec.).

Example 293.

3 - [2 - {4 - (3 - carboxy - 3 - phthalimidopropoxy)phenyl} - 2 - hydroxyiminoacetamido]lactacillanic acid (4.2 g.) was dissolved in methanol (40 ml.). A solution, prepared by dissolving sodium hydrogen sulfite (4.2 g.) in water (80 ml.), was added to the solution, and the mixed solution was heated for 3.5 hrs. under reflux. Subsequently, the reaction mixture was concentrated to a volume of about 30 ml., and the concentrate was adjusted to pH 2.0 with 10% hydrochloric acid under ice-cooling, and then the solution was extracted with ethyl acetate. The extract was washed with water and dried, and then the solvent was distilled off from the extract to give 3-[4-(3-carboxy-3-phthalimidopropoxy)phenylglyoxyloylamino]lactacillanic acid (2.1 g.). Mp 115 to 120°C (dec.).

Example 294.

3 - [2 - [4 - {3 - Carboxy - 3 - (3 - phenylureido)propoxy}phenyl] - 2 - hydroxyiminoacetamido]lactacillanic acid was treated in substantially the similar manner as described in Example 293 to give 3-[4-{3-carboxy-3-(3-phenylureido)propoxy}phenylglyoxyloylamino]lactacillanic acid. Mp 100 to 106°C (dec.).

Example 295.

3 - [2 - {4 - (3 - Amino - 3 - carboxypropoxy)phenyl} - 2 - hydroxyiminoacetamido]lactacillanic acid (0.5 g.) was suspended in an aqueous solution (10 ml.) of ammonium acetate (1.93 g.), and 28% ammonia water (0.3 ml.) and zinc powder (0.435 g.) were added to the solution, whereafter the mixture was stirred for 24 hrs. at ambient temperature. The reaction mixture was adjusted to pH 4 with 1N-hydrochloric acid, and hydrogen sulfide gas was introduced into the solution, and then the insoluble material was filtered off. The filtrate was concentrated under reduced pressure to give a residue, and the residue was dissolved in water (10 ml.), and then to the solution was added ethanol (200 ml.). The forming precipitate was collected by filtration, and dried to give 3-[2-{4-(3-amino-3-carboxypropoxy)phenyl}glycinamido]lactacillanic acid (420 mg.). Mp 206 to 208°C (dec.).

Example 296.

N,N-Dimethylformamide (0.5 ml.), formic acid (0.5 ml.) and zinc powder (1.0 g) were added to a solution containing 3-[2-{4-(3-phthalimido-3-carboxypropoxy)-phenyl}-2-hydroxyiminoacetamido]lactacillanic acid (1.00 g.), methanol (8 ml.) and water (2 ml.), and the mixture was stirred for 4 hrs. The zinc powder was filtered off from the reaction mixture, and hydrogen sulfide was introduced into the filtrate, and then the insoluble material was filtered off. The filtrate was concentrated under reduced pressure, to give a residue which was powdered with acetone to give 3-[2-{4-(3-phthalimido-3-carboxypropoxy)phenyl}glycinamido]lactacillanic acid (0.68 g.). Mp 215 to 219°C (dec.).

Example 297.

10% Palladium : carbon (0.6 g.) was added to a solution containing 3-[2-{4-(3-acetamido - 3 - carboxypropoxy)phenyl} - 2 - hydroxyiminoacetamido]lactacillanic acid (1.85 g.), sodium bicarbonate (0.6 g.) and water (20 ml.). The mixture was subjected to absorption of a calculated volume of hydrogen gas at ordinary temperature and ordinary atm. The catalyst was filtered off from the reaction mixture, and the filtrate was adjusted to pH 3 with 10% hydrochloric acid under ice-cooling, and then treated with an activated carbon. The aqueous solution obtained was crystallized from acetone (150 ml.) under ice-cooling. The crystals were collected by filtration, and

washed with water (10 ml.) and acetone, respectively to give 3-[2-{4-(3-acetamido-3-carboxypropoxy)phenyl}glycinamido]lactacillanic acid (0.38 g.). Furthermore, the washing obtained above was crystallized from acetone (10 ml.) under ice-cooling, and the crystals were washed with acetone, and then collected by filtration to recover a object compound (0.32 g.). Total yield was 0.70 g. Mp 198 to 204°C (dec.).

Example 298.

10% Palladium : carbon (3 g.) was added to a solution of 3-[2-{4-(3-benzamido-3-carboxypropoxy)phenyl}-2-hydroxyiminoacetamido]lactacillanic acid (10.0 g.), sodium bicarbonate (2.79 g.) and water (70 ml.), and the mixture was subjected to a catalytic reduction for 5 hrs. under shaking enough under 3 atm at ordinary temperature. After the reaction, the catalyst was filtered off from the reaction mixture, and the filtrate was adjusted to pH 3.0 with 10% hydrochloric acid under ice-cooling to give crystals of 3-[2-{4-(3-benzamido-3-carboxypropoxy)phenyl}glycinamido]lactacillanic acid (7.8 g.). Furthermore, a object compound (0.4 g.) was recovered from the mother liquor. Total yield was 8.2 g. Mp 171 to 176°C (dec.).

Example 299.

3 - [4 - (3 - Carboxy - 3 - phthalimidopropoxy)phenylglyoxyloylamino]lactacillanic acid (1.10 g.) was suspended in water (11 ml.), and to the suspension was added sodium bicarbonate (0.40 g.) to dissolve it. To the solution was added sodium borohydride (0.08 g.) under ice-cooling, and the mixture was stirred for 4 hrs. at the same temperature. The reaction mixture was adjusted to pH 2 with 10% hydrochloric acid to give crystals of 3-[2-{4-(3-carboxy-3-phthalimidopropoxy)phenyl}-2-hydroxy acetamido]lactacillanic acid (0.91 g.). Mp 160 to 163°C (dec.).

Example 300.

Acetic acid anhydride (20 ml.) was added to a suspension, prepared by suspending 3 - [2 - {4 - (3 - amino - 3 - carboxypropoxy)phenyl} - 2 - hydroxyiminoacetamido]-lactacillanic acid (10 g.) in methanol (150 ml.), and the mixture was stirred for 4.5 hrs. The reaction mixture was concentrated under reduced pressure to give a residue, to which was added toluene. The solution was concentrated under reduced pressure again to give a residue which was powdered by adding ethyl acetate to give 3-[2-{4-(3-acetamido - 3 - carboxypropoxy)phenyl} - 2 - hydroxyiminoacetamido]lactacillanic acid (10.3 g.). Mp 90 to 93°C (dec.).

Example 301.

Acetic acid anhydride (6 ml.) was added to a methanol suspension (60 ml.) of 3 - [4 - (3 - amino - 3 - carboxypropoxy)phenylglyoxyloylamino]lactacillanic acid (3.0 g.) under ice-cooling, and the mixture was stirred for 1 hour at the same temperature, and further stirred for 4 hrs. at ambient temperature. The reaction mixture was concentrated under reduced pressure, and the concentrate was powdered with ether to give 3 - [4 - (3 - acetamido - 3 - carboxypropoxy)phenylglyoxyloylamino]lactacillanic acid (2.26 g.). Mp 96 to 102°C (dec.).

Example 302.

3 - [2 - {4 - (3 - Amino - 3 - carboxypropoxy)phenyl}glycinamido]lactacillanic acid was treated in substantially the similar manner as described in Example 301 to give 3 - [2 - {4 - (3 - acetamido - 3 - carboxypropoxy)phenyl} - N - acetylglycinamido]lactacillanic acid.

I.R. absorption spectrum,

ν cm^{-1} (Nujol): 1735, 1650.

Example 303.

3 - [2 - {4 - (3 - Amino - 3 - carboxypropoxy)phenyl} - 2 - hydroxyiminoacetamido]lactacillanic acid (0.50 g.) was suspended in dried methylene chloride (20 ml.). To the suspension was added N,O-bis(trimethylsilyl)acetamide (1.50 g.), and the mixture was stirred for 2 hrs. at ambient temperature, and then heated for 10 minutes under reflux. The reaction solution was cooled to 0 to 5°C, and triethylamine (0.12 g.) and 2,2,2-trifluoroacetic acid anhydride (0.27 g.) were added to the solution, and then the reaction solution was stirred for 1 hour. The methylene chloride was distilled off from the reaction mixture to give a residue which was dissolved in ethyl acetate (20 ml.). The solution was washed with 2% hydrochloric acid five times, with water twice and with a sodium chloride-saturated-aqueous solution once, respectively, and then dried over anhydrous magnesium sulfate. The solvent was distilled off from the

solution, and benzene was added to the residue to give powdery crystals of 3-[2-[4-{3-carboxy - 3 - (2,2,2 - trifluoroacetamido)propoxy}phenyl] - 2 - hydroxyiminoacetamido]lactacillanic acid (0.41 g.). Mp 143 to 147°C (dec.).

Example 304.

N,O-Bis(trimethylsilyl)acetamide (15 ml.) was added to a suspension, prepared by suspending 3 - [4 - (3 - amino - 3 - carboxypropoxy)phenylglyoxyloylamino]-lactacillanic acid (4.0 g.) in dried methylene chloride (80 ml.), and the mixture was stirred for 2 hrs. to dissolve the starting material completely. To the solution was added triethylamine (0.88 g.) under ice-cooling, and then a solution, prepared by dissolving 2,2,2-trifluoroacetic acid anhydride (1.9 g.) in methylene chloride (5 ml.), was added dropwise to the solution during 30 minutes. The reaction mixture was stirred for 1.5 hrs. at the same temperature, and then the methylene chloride was distilled off from the reaction mixture under reduced pressure, whereafter the residue was poured into a mixture of ice-water (50 ml.) and ethyl acetate (100 ml.). The ethyl acetate layer separated out was dried over anhydrous magnesium sulfate, and then the solvent was distilled off to give a residue to which was added benzene to give powdery crystals of 3-[4-{3-carboxy - 3 - (2,2,2 - trifluoroacetamido)propoxy}phenylglyoxyloylamino]lactacillanic acid (3.0 g.).

I.R. absorption spectrum,

ν cm^{-1} (Nujol): 1730, 1680.

Example 305.

3 - [2 - {4 - (3 - Amino - 3 - carboxypropoxy)phenyl} - 2 - hydroxyiminoacetamido]lactacillanic acid (20.0 g.) was suspended in a mixture of water (200 ml.) and acetone (200 ml.), followed by adding sodium bicarbonate (6.8 g.) to dissolve it. Benzoyl chloride (6.7 g.) was added dropwise to the solution under ice cooling, keeping the solution in pH 8.0. The reaction mixture was stirred for 4 hrs. and the acetone was distilled off from the reaction mixture. The remaining aqueous solution was washed with ethyl acetate, and ethyl acetate (400 ml) was added to the solution. The mixture was adjusted to pH 2.0 with 10% hydrochloric acid under cooling and then the ethyl acetate layer was separated out, and washed with water and with a sodium chloride-saturated-aqueous solution, respectively, and dried. The ethyl acetate was distilled off from the solution to give a residue, followed by suspending in water (200 ml.). 1N-Sodium hydroxide aqueous solution (160 ml.) was added to the suspension, and the solution was stirred for 2 hrs. Ethyl acetate (400 ml.) was added to the solution, and the mixture was adjusted to pH 2.0 with 10% hydrochloric acid under ice-cooling. The ethyl acetate layer separated out was washed with water and dried. The solvent was distilled off from the solution to give the powder (21.6 g.) which was crystallized from a mixture of acetone and benzene to give crystals of 3-[2-{4-(3-benzamido-3-carboxypropoxy)phenyl}-2-hydroxyiminoacetamido]lactacillanic acid (10.4 g.). Mp 170 to 172°C (dec.).

Example 306.

3 - [4 - (3 - Amino - 3 - carboxypropoxy)phenylglyoxyloylamino]lactacillanic acid (970 mg.) was suspended in water (10 ml.), and the suspension was adjusted to pH 8 to 9 with 1N-sodium hydroxide aqueous solution under ice-cooling. An acetone solution (10 ml.) of phenyl isocyanate (360 mg.) was added dropwise to the solution, keeping the solution at pH 8 to 9 during adding dropwise. The solution was stirred for an hour, and the diphenylurea produced as a by-product was filtered off from the solution. The filtrate was adjusted to pH 1 to 2 with 10% hydrochloric acid and then extracted with ethyl acetate. The extract was washed with a sodium chloride-saturated-aqueous solution, and dried over anhydrous magnesium sulfate, whereafter the solvent was distilled off from the solution to give crystals of 3-[4-{3-carboxy-3-(3-phenylureido)propoxy}-phenylglyoxyloylamino]lactacillanic acid (1.33 g.). Mp 100 to 106°C (dec.).

Example 307.

3 - [2 - {4 - (3 - Amino - 3 - carboxypropoxy)phenyl}glycinamido]lactacillanic acid (250 mg.) was suspended in water (5 ml.), and the suspension was adjusted to pH 8 with 1N-sodium hydroxide aqueous solution to dissolve it under ice-cooling. A dried acetone solution (2 ml.) of phenyl isocyanate (150 mg.) was added to the solution under cooling, keeping the solution in pH 8 to 9 during the addition. The solution was stirred for an hour under ice-cooling, and then adjusted to pH 2 with 10% hydrochloric acid to give a precipitate. The precipitate was collected by filtration and washed with water, and then dissolved in a sodium bicarbonate aqueous solution. An insoluble materials were filtered off, and the filtrate was adjusted to pH 1 to 2 with 10% hydro-

chloric acid to give crystals which were collected by filtration, washed with water and then dried on phosphorus pentachloride to give crystals of 3-[2-[4-{3-carboxy-3-(3-phenylureido)propoxy}phenyl] - 2 - (3 - phenylureido)acetamido]lactacillanic acid (0.35 g.). Mp 170 to 172°C (dec.).

Example 308.

A suspension of 3-[2-{4-(3-amino-3-carboxypropoxy)phenyl}-2-hydroxyimino-acetamido]lactacillanic acid (10 g.), water (100 ml.) and acetone (30 ml.) was adjusted to pH 8 to 9 with 1N-sodium hydroxide aqueous solution under ice-cooling. To the solution was added dropwise an acetone solution (5 ml.) of phenyl isocyanate (2.9 g.) at the same temperature, and the mixture was stirred for an hour. The acetone was distilled off from the reaction mixture under reduced pressure, and the remaining solution was adjusted to pH 2 with 10% hydrochloric acid, and extracted with ethyl acetate. The extract was washed with diluted hydrochloric acid and water, respectively, and dried. The ethyl acetate was distilled off from the solution to give a residue which was crystallized from ether (100 ml.) to give crystals of 3-[2-[4-{3-carboxy-3-(3-phenylureido)propoxy}phenyl]-2-hydroxyiminoacetamido]lactacillanic acid (10.3 g.). Mp 135 to 139°C (dec.).

Example 309.

An acetone solution (5 ml.) containing ethyl phthalimidoformate (0.60 g.) was added dropwise to a solution containing 3-[2-{4-(3-amino-3-carboxypropoxy)phenyl}-2-hydroxyiminoacetamido]lactacillanic acid (0.94 g.), 10% a dipotassium hydrogen-phosphate aqueous solution (20 ml.) and acetone (10 ml.), and the mixture was stirred for 2 hrs., keeping the mixture in pH 8. The acetone was distilled off from the reaction mixture under reduced pressure, and the remaining solution was adjusted to pH 2 with diluted hydrochloric acid, and then extracted with ethyl acetate. The extract was washed with water and dried over anhydrous magnesium sulfate. The ethyl acetate was distilled off from the solution to give residue, which was crystallized from an ethanol aqueous solution to give crystals of 3-[2-{4-(3-carboxy-3-phthalimidopropoxy)phenyl}-2-hydroxyiminoacetamido]lactacillanic acid (0.69 g.). Mp 160 to 165°C (dec.).

Example 310.

3 - [2 - {4 - (3 - Amino - 3 - carboxypropoxy)phenyl}glycolamido]lactacillanic acid was treated in substantially the similar manner as described in Example 309 to give crystals of 3-[2-{4-(3-carboxy-3-phthalimidopropoxy)phenyl}glycolamido]lactacillanic acid. Mp 160 to 163°C (dec.).

Example 311.

3-[4-(3-Amino-3-carboxypropoxy)phenylglyoxyloylamino]lactacillanic acid was treated in substantially the similar manner as described in Example 309 to give crystals of 3-[4-(3-carboxy-3-phthalimidopropoxy)phenylglyoxyloylamino]lactacillanic acid. Mp 216°C (dec.).

Example 312.

Phenyl isothiocyanate (320 mg.) was added to a 50% pyridine aqueous solution (6 ml.) of 3-[2-{4-(3-amino-3-carboxypropoxy)phenyl}glycinamido]lactacillanic acid (250 mg.) at 40°C under stirring. The mixture was stirred for an hour, keeping the mixture in pH 8 to 9 with a sodium bicarbonate-saturated-aqueous solution. The reaction mixture was washed with ether, and the aqueous layer was separated out, and then adjusted to pH 1 to 2 with 10% hydrochloric acid under cooling to give crystals of 3 - [2 - [4 - {3 - carboxy - 3 - (3 - phenylthioureido)propoxy}phenyl] - 2 - (3-phenylthioureido)acetamido]lactacillanic acid (250 mg.). Mp 190 to 195°C (dec.).

Example 313.

3 - [2 - {4 - (3 - Amino - 3 - carboxypropoxy)phenyl}glycinamido]lactacillanic acid (2.0 g.) was suspended in a 50% pyridine aqueous solution (20 ml.), and the suspension was adjusted to pH 8.6 with 1N-sodium hydroxide aqueous solution to dissolve it. To the solution was added 1-naphthyl isothiocyanate (1.94 g.), and the mixture was stirred for 4 hrs. The reaction mixture was washed with ether and adjusted to pH 2.0 with 10% hydrochloric acid under cooling to give a precipitate. The precipitate was collected by filtration and washed with water. The Precipitate was dissolved in a sodium bicarbonate-saturated-aqueous solution, and 10% hydrochloric acid was added to the solution to give crystals of 3 - [2 - [4 - [3 - carboxy - 3 - {3 - (1 - naphthyl)thioureido}propoxy]phenyl] - 2 - {3 - (1 - naphthyl)thioureido}acetamido]lactacillanic acid (2.7 g.). Mp 169 to 173°C (dec.).

Example 314.

3 - [2 - {4 - (3 - Amino - 3 - carboxypropoxy)phenyl}glycinamido]lactacillanic acid (480 mg.) was suspended in water (10 ml.), and to the suspension was added 1N-potassium hydroxide aqueous solution (5 ml.) under ice-cooling, while stirring. An acetone (5 ml.) solution of O-ethyl-S-methyl dithiocarbonate (0.72 g.) was added to the solution, and then the mixture was stirred for 5 hrs. at ambient temperature. The reaction mixture was washed with ether, and the remaining aqueous layer was separated out. The aqueous solution was adjusted to pH 1 to 2 with 10% hydrochloric acid and extracted with ethyl acetate, and then the extract was washed with water and dried. The solvent was distilled off from the solution to give 3 - [2 - [4 - {3 - carboxy - 3-ethoxy(thiocarbonyl)aminopropoxy}phenyl] - 2 - ethoxy(thiocarbonyl)aminoacetamido]lactacillanic acid (230 mg.). Mp 112 to 119°C (dec.).

Example 315.

3 - [2 -{ 4 - (3 - Amino - 3 - carboxypropoxy)phenyl} - 2 - hydroxyiminoacetamido]lactacillanic acid (1.0 g.) was dissolved in a mixture of 0.1N-sodium hydroxide aqueous solution (40 ml.) and acetone (15 ml.). To the solution were added dropwise an acetone (5 ml.) solution containing 2-(4-chloro-2-nitrophenoxy)acetyl chloride (550 mg.) and 0.1 N-sodium hydroxide aqueous solution (40 ml.) at the same time under ice-cooling, while stirring. The mixture (pH 9.2 to 9.4) was stirred for 40 minutes at the same temperature, and further stirred for 40 minutes at ambient temperature. The reaction mixture was washed with ethyl acetate, and then ethyl acetate was added to the aqueous layer, whereafter the mixture was adjusted to pH 2 with 10% hydrochloric acid. The ethyl acetate layer was separated out, washed with water and dried over anhydrous magnesium sulfate. The solvent was distilled off from the solution to give a residue which was washed with ether several times. The residue was dissolved in ethyl acetate under warming, and an insoluble material was filtered off and then to the solution was added chloroform to give a powder which was collected by filtration to give 3 - [2 - [4 - [3 - {2 - (4 - chloro - 2 - nitrophenoxy)acetamido} - 3 - carboxypropoxy]phenyl] - 2 - hydroxyiminoacetamido]lactacillanic acid (150 mg.). Furthermore, an object compound (30 mg.) was obtained from the mother liquor. Total yield was 180 mg. Mp 145 to 150°C (dec.).

Example 316.

An acetone (4 ml.) solution containing 2-(2-thienyl)acetyl chloride (352 mg.) was added dropwise to a solution containing 3 - [2 - {4 - (3 - amino - 3 - carboxypropoxy)phenyl} - 2 - hydroxyiminoacetamido]lactacillanic acid (1.0 g.), sodium bicarbonate (504 mg.), water (30 ml.) and acetone (10 ml.) under ice-cooling, while stirring, keeping the solution in pH 8. The mixture was stirred for 40 minutes at the same temperature, and further stirred for 30 minutes ambient temperature. The reaction mixture was washed with ethyl acetate, and then ethyl acetate was added to the solution, whereafter the mixture was adjusted to pH 2 with 10% hydrochloric acid. The ethyl acetate layer was separated out, and the remaining aqueous layer was extracted with ethyl acetate. These ethyl acetate layers were combined and washed with a sodium chloride-saturated-aqueous solution, and then dried over anhydrous magnesium sulfate. The solvent was distilled off from the solution, and the residue (740 mg.) obtained was added to 0.1 N-sodium hydroxide aqueous solution (30 ml.). The solution (pH 9.4) was stirred for an hour at ambient temperature, and washed with ethyl acetate, and to the solution was added ethyl acetate. The mixture was adjusted to pH 2 by adding 10% hydrochloric acid and then treated in the similar manner as described above to give a residue (450 mg.). The residue was dissolved in a mixture of acetone and n-hexane, and the solution was treated with activated carbon, followed by filtration. The filtrate was concentrated to give a residue which was washed with ether several times and with n-hexane once to give 3 - [2 - [4 - [3 - carboxy - 3 - {2 - (2 - thienyl)acetamido}-propoxy]phenyl] - 2 - hydroxyiminoacetamido]lactacillanic acid (400 mg.), mp 145 to 150°C (dec.).

Example 317.

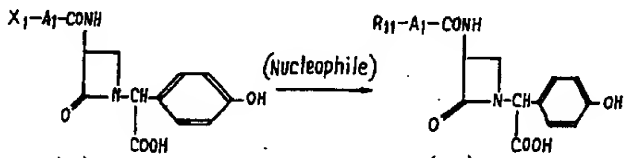
An acetone (25 ml.) solution containing α-ethoxycarbonyloxycarbonyl-α-toluenesulfonic acid triethylamine salt (3.1 g.) and an aqueous solution (10 ml.) of sodium bicarbonate (756 mg.) were added dropwise to a solution containing 3-[2-{4-(3-amino-3-carboxypropoxy)phenyl}-2-hydroxyiminoacetamido]lactacillanic acid (2.0 g.), sodium bicarbonate (756 mg.), water (35 ml.) and acetone (15 ml.) during 15 minutes under ice-cooling. The reaction mixture (pH 7.6) was stirred for 30 minutes at the same temperature, and further stirred for 30 minutes at ambient temperature. The acetone was distilled off from the reaction mixture, and the remaining solution was

adjusted to pH 3 with 10% hydrochloric acid, whereafter the solution was washed with ethyl acetate. The ethyl acetate layer was separated out, and the remaining aqueous solution was adjusted to pH 1 with 10% hydrochloric acid, and extracted with n-butyl alcohol. The extract obtained was washed with 5% hydrochloric acid once and with a sodium chloride-saturated-aqueous solution once, respectively, and dried over anhydrous magnesium sulfate. The extract was adjusted to pH 6 with an acetone (21 ml.) solution containing sodium 2-ethylhexanate (11 mg.) to give a powder which was collected by filtration. The powder was washed with acetone to give the colorless powder (2.3 g.). A part of the powder (1.0 g.) was dissolved in water (3 ml.), and the solution was adjusted to pH 3 with 10% hydrochloric acid, and then washed with ethyl acetate, whereafter the solution was subjected to column chromatography using a nonionic adsorption resin, Amberlite XAD—2 (trade mark, maker; Rohm and Haas Co. Ltd.,), and the compound eluted with water was lyophillized to give 3-[2-[4-{3-carboxy-3-(2-phenyl-2-sulfoacetamido)propoxy}phenyl]-2-hydroxyiminoacetamido]lactacillanic acid sodium salt (350 mg.). Furthermore, an object compound (480 mg.) was recovered from the fractions, eluted with water containing methanol (20%) and methanol. Total yield was 830 mg. Mp 244 to 250°C (dec.).

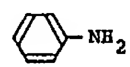
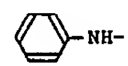
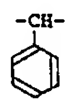
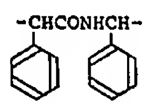
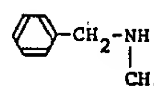
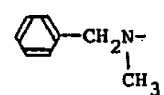
Example 318.

Potassium carbonate (0.127 g.) and water (3 ml.) were added to an acetone solution (3 ml.) containing N-methylaniline (0.200 g.), and the solution was stirred at 25 to 28°C. To the solution was added dropwise a mixture (4 ml.) of acetone and water (1:1) containing 3-(2-bromoacetamido)lactacillanic acid (0.321 g.) and sodium bicarbonate (0.067 g.), and the reaction mixture was reacted for 17 hrs. at the same temperature. The acetone was distilled off from the reaction mixture under reduced pressure, and the remaining aqueous layer was washed with ethyl acetate. The aqueous layer was adjusted to pH 3 with diluted hydrochloric acid, and then extracted with ethyl acetate. The extract was washed with water, dried and then concentrated. The residue obtained was crystallized from methanol to give crystals of 3-(N-methyl-N-phenylglycinamido)-lactacillanic acid (0.208 g.). Mp 198 to 199°C (dec.).

The following compounds were obtained in substantially the similar manner as described above.



(XI) (XII)

Example	Compound (XI)		Nucleophile	Compound (XII)		
	X_1-	-A_1-		R_{11}	-A_1-	mp(°C). (dec.)
319	Br-	-CH_2-			the same as A_1 of the Compound (XI)	193 - 194.5
320	"		"	"	"	97 - 101
321	"		"	"	"	158 - 161
322	"	-CH_2-			"	154 - 157

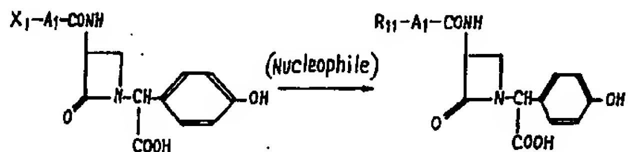
Example 323.

Morpholine (0.262 g.) was dissolved in a mixture (5 ml.) of acetone and water (1:1), and to the solution was added potassium carbonate (0.180 g.). The solution was cooled to 10°C, and to the solution was added dropwise a mixture (5 ml.) of acetone and water (1:1) containing 3-(2-bromoacetamido)lactacillanic acid (0.464 g.) and sodium bicarbonate (0.110 g.). The reaction mixture was reacted for 5 hrs., keeping the reaction temperature at 10 to 20°C. The acetone was distilled off from the reaction mixture under reduced pressure, and the remaining aqueous solution was washed with ethyl acetate. The aqueous solution was adjusted to pH 1 to 2 with diluted hydrochloric acid and washed with ethyl acetate. The aqueous solution was adjusted to pH 4.5 to 4.8 with sodium bicarbonate, and the solution was concentrated under reduced pressure, and then the residue was extracted with methanol. The extract was concentrated to give an oily material which was dissolved in a small amount of methanol. Acetone was added to the solution, which was filtered. The filtrate was concentrated to give an oily material (0.38 g.) which was subjected to column chromatography using a nonionic adsorption resin, Amberlite XAD—2 (trade mark, maker; Rohm and Haas Co., Ltd.) (35 ml.). Isolation and purification were carried out. Fractions eluted with water were collected and the water was distilled off from the eluate to give crystals of 3-(2-morpholinoacetamido)lactacillanic acid (0.38 g.). Mp 201 to 203°C (dec.).

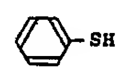
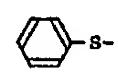
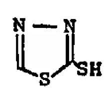
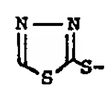
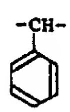
Example 324.

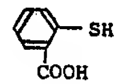
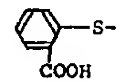
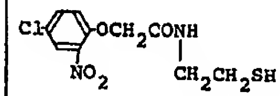
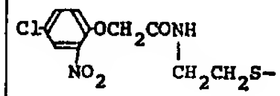
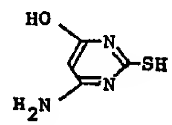
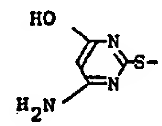
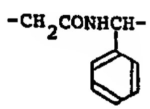
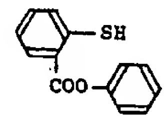
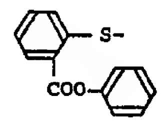
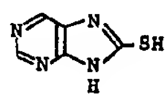
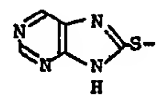
A mixture containing 3-[2-(2-bromoacetamido)-2-phenylacetamido]lactacillanic acid (196 mg.) 2-mercaptobenzoic acid (62 mg.) and 0.1N-sodium hydroxide aqueous solution (12 ml.) was stirred for an hour at ambient temperature. The reaction mixture (pH 6.8 to 7.8) was adjusted to pH 3 with 1N-hydrochloric acid (0.4 ml.) and washed with ether and then further adjusted to pH 1 to 2 with 1N-hydrochloric acid. The solution was extracted with ethyl acetate and the extract was washed with water and dried over anhydrous magnesium sulfate. The solution was concentrated to a volume of about 4 ml. under reduced pressure to give crystals which were washed with ether to give crystals of 3-[2-{2-(2-carboxyphenylthio)acetamido}-2-phenylacetamido]-lactacillanic acid (125 mg.). Furthermore, an object compound (50 mg.) was recovered from the filtrate. Total yield was 175 mg. Mp 143 to 146°C (dec.).

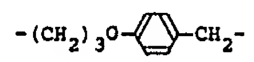
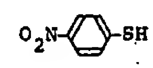
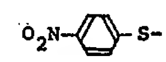
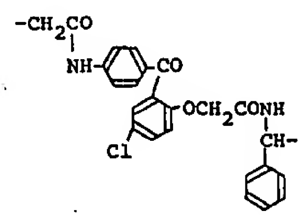
The following compounds were obtained in substantially the similar manner as described above.



(XI) (XII)

Example	Compound (XI)		Nucleophile	Compound (XII)		
	X_1-	-A_1-		R_{11}-	-A_1-	mp(°C) (dec.)
325	Br-	$-CH_2-$	CH_3SH	CH_3S-	the same as A_1 of the Compound (XI)	154 - 155
326	"	"	$CH_2=CHCH_2SH$	$CH_2=CHCH_2S$-	"	178 - 183
327	"	"			"	183 - 185
328	"	"			"	163 - 167
329	"		CH_3SH	CH_3S-	"	159 - 162

330	"	"			"	90 - 95
331	"	"			"	77 - 81
332	"	"			"	124 - 128
333	"	"			"	217 - 221
334	"				"	141 - 146
335	"	"			"	192 - 197

336	"				"	142 - 146
337	"		HOOC-CH_2SH	HOOC-CH_2S-	"	141 - 144
338	"	"	HOOC-CH(NH_2·HCl)CH_2SH	HOOC-CH(NH_2)CH_2S-	"	202 - 206
339	"	"	H_2N-CH_2CH_2SH	$H_2NCH_2CH_2$S-	"	191 - 196

Example 340.

3-(2-Bromo-2-phenylacetamido)lactacillanic acid (86 mg.) and cysteine hydrochloride (one hydrate) (35 mg.) were suspended in water (3 ml.), and to the suspension was added 1N-sodium hydroxide aqueous solution (0.4 ml.) under ice-cooling, while stirring. The solution was reacted for about 3 hrs. and then the mixture was adjusted to pH 8, followed by being reacted for 2 hrs. The reaction mixture was adjusted to about pH 2 with 1N-hydrochloric acid and then filtered. The filtrate was adjusted to pH 8 to 9 with a sodium bicarbonate aqueous solution, and then concentrated to give a residue which was subjected to column chromatography using a nonionic adsorption resin, Amberlite XAD—2 (trade mark, maker; Rohm and Haas Co., Ltd.) (20 ml.) which had been washed previously with methanol and water. The fractions, obtained by being eluted with water, were collected and the eluate was evaporated to give crystals of 3-[2-(2-amino-2-carboxyethylthio)-2-phenylacetamido]lactacillanic acid disodium salt of carboxy group (20 mg.). Mp 211 to 216°C dec.).

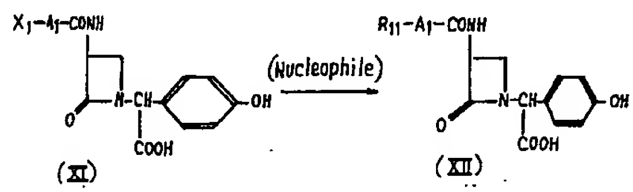
Example 341.

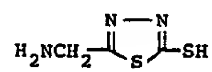
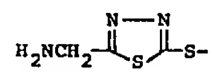
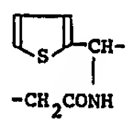
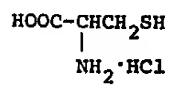
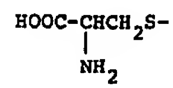
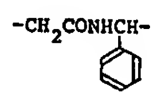
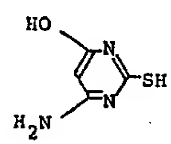
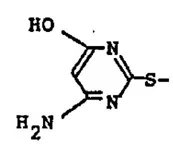
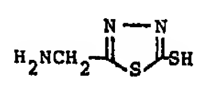
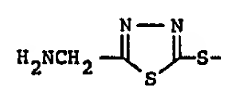
3-(2-Bromo-2-phenylacetamido)lactacillanic acid (150 mg.) and 2-aminoethanethiol (35 mg.) were treated in substantially the similar manner as described in Example 340 to give crystals of 3-[2-(2-aminoethylthio)-2-phenylacetamido]lactacillanic acid sodium salt (54 mg.). Mp 171 to 173°C (dec.).

Example 342.

A mixture of 3-(2-bromoacetamido)lactacillanic acid (107 mg.), water (3 ml.) and 1N-potassium hydroxide aqueous solution (0.6 ml.) was added dropwise to a solution containing cysteine hydrochloride (38 mg.), water (3 ml.) and 1N-potassium hydroxide aqueous solution (0.9 ml.) under ice-cooling while stirring, and then the solution was reacted for an hour at the same temperature. The reaction mixture was adjusted to about pH 4 with 1N-hydrochloric acid (0.9 ml.), and concentrated under reduced pressure to give a residue which was dissolved in methanol. The solution was subjected to column chromatography using a nonionic adsorption resin, Amberlite XAD—2 (trade mark, maker; Rohm and Haas Co., Ltd.). Fractions eluted with water were collected, and evaporated to give crystals of 3-[2-(2-amino-2-carboxyethylthio)-acetamido]lactacillanic acid (95 mg.). Mp 105 to 110°C (dec.).

The following compounds were obtained in substantially the similar manner as described above.



Example	Compound (XI)		Nucleophile	Compound (XII)		
	X_1-	-A_1-		R_{11}-	-A_1-	mp(°C) (dec.)
343	Br-	$-CH_2-$	$H_2NCH_2CH_2SH$ HCl	$H_2NCH_2CH_2S$-	the same as A_1 of the compound (XI)	171 - 175
344	"	"	 HCl		"	176 - 180
345	"				"	187 - 192
346	"				"	230 - 235
347	"	"			"	196 - 199

Example 348.

Sodium pyridine-1-oxide-2-thiolate (60 mg.) was added to a mixture of 3-[2-(2-bromoacetamido)-2-phenylacetamido]lactacillanic acid (200 mg.) and 0.1N-sodium hydroxide aqueous solution (4 ml.) under ice-cooling, and the mixture was stirred for 30 minutes. Ethyl acetate was added to the reaction mixture, and the solution was adjusted to pH 1 to 2 with 10% hydrochloric acid to give a precipitate which was collected by decantation. The precipitate was dried and washed with acetone to give 3 - [2 - {2 - (pyridyl - 1 - oxide - 2 - thio)acetamido} - 2 - phenylacetamido]lactacillanic acid (82 mg.). Furthermore, the acetone washing was concentrated to give a residue which was washed with diisopropyl ether to recover an object compound (33 mg.). Total yield was 115 mg. Mp 160 to 164°C (dec.).

Example 349.

3-(2-Bromoacetamido)lactacillanic acid (285 mg.) and sodium pyridine-1-oxide-2-thiolate (120 mg.) were treated in substantially the similar manner as described in Example 348 to give 3-[2-(pyridyl-1-oxide-2-thio)acetamido]lactacillanic acid (250 mg.). Mp 221 to 225°C (dec.).

Example 350.

8-Mercapto-9H-purine (76 mg.) was added to a mixture of 3-[2-phenyl-2-(2-phenylsulfoacetamido)acetamido]lactacillanic acid (285 mg.) and 0.1N-sodium hydroxide aqueous solution (10 ml.) under ice-cooling. After the reaction temperature was elevated to ambient temperature, the reaction mixture was stirred for 3 hrs. To the reaction mixture was added 1N-hydrochloric acid (0.5 ml.) to give a precipitate which was collected by filtration. The precipitate was washed with water and dried to give 3 - [2 - phenyl - 2 - {2 - (9H - purin - 8 - yl - thio)acetamido}acetamido]lactacillanic acid (120 mg.) Mp 192 to 197°C (dec.).

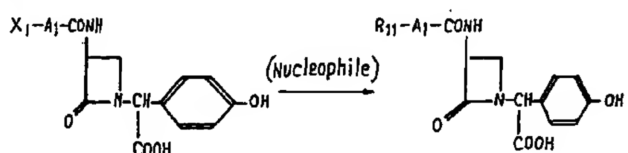
Example 351.

Sodium hydride (50% oily) (9.6 mg.) and phenol (19 mg.) were added to anhydrous N,N-dimethylformamide (2 ml.), and the mixture was stirred for 30 minutes, and then ice-cooled. To the solution was added all at once 3-[2-phenyl-2-(2-bromoacetamido)acetamido]lactacillanic acid (50 mg.), and the reaction mixture was stirred for an hour at the same temperature and further stirred for an hour at ambient temperature. Ether (10 ml.) was added to the reaction mixture to give a precipitate which was collected by filtration. The precipitate was dissolved in a small amount of water, and the solution was adjusted to pH 1 with 10% hydrochloric acid, and then extracted with ethyl acetate. The extract was washed with water and dried over anhydrous magnesium sulfate, and then the solvent was distilled off from the solution. The residue was powdered with ether, and collected by filtration and washed with ether sufficiently to give 3-[2-phenyl-2-(2-phenoxyacetamido)acetamido]lactacillanic acid (10 mg.).

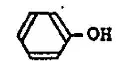
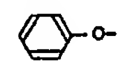
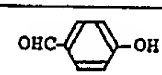
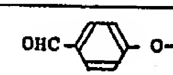
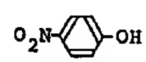
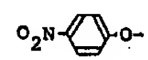
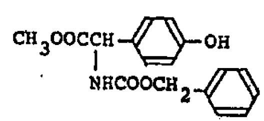
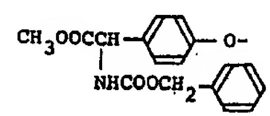
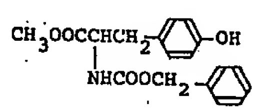
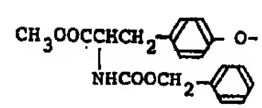
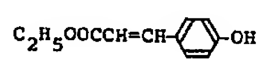
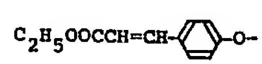
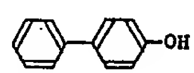
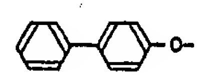
I.R. absorption spectrum,

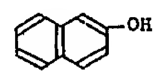
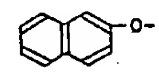
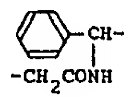
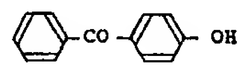
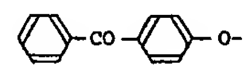
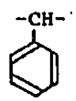
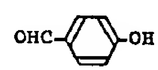
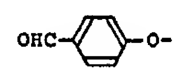
ν cm^{-1} (Nujol): 1740, 1720, 1650.

The following compounds were obtained in substantially the similar manner as described above.



(XI) (XII)

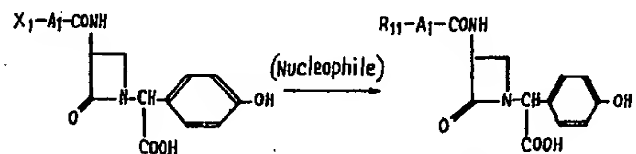
Example	Compound (XI)		Nucleophile	Compound (XII)		
	X_1^- •	$-A_1-$		$R_{11}-$	$-A_1-$	mp(°C) (dec.)
352	Br-	$-CH_2-$			the same as $A_1$of the Compound (XI)	180 - 184
353	"	"			"	145 - 146
354	"	"			"	137 - 140
355	"	"			"	80 - 85
356	"	"			"	136 - 140
357	"	"			"	109 - 110
358	"	"			"	195 - 198

359	"	"			"	143 - 146
360	"				"	154 - 159
361	"				"	95 - 96

Example 362.

3 - [2 - [2 - [2 - {4 - (2 - Chloroacetamido)benzoyl} - 4 - chlorophenoxy]acetamido] - 2 - phenylacetamido]lactacillanic acid (150 mg.) and pyridine - 2 - thiol (25 mg.) was treated in substantially the similar manner as described in Example 324 to give 3 - [2 - [2 - [2 - [4 - {2 - (pyridin - 2 - yl - thio)acetamido}benzoyl] - 4-chlorophenoxy]acetamido] - 2 - phenylacetamido]lactacillanic acid (120 mg.). Mp 109—114°C (dec.).

The following compounds were obtained in substantially the similar manner as described in Example 342.



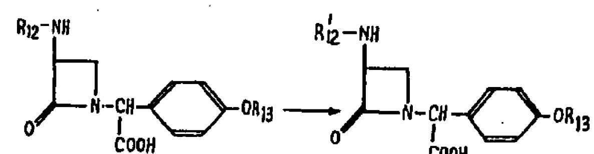
(XI) (XII)

Example	Compound (XI)		Nucleophile	Compound (XII)		
	X_1-	-A_1-		R_{11}-	-A_1-	mp (°C) (dec.)
363	Br-	$-CH_2CONHCH_2$-(o-phenylene)-OCH_2-	H_2N-$CH(COOH)CH_2$-SH	H_2N-$CH(COOH)CH_2$-S-	the same as A_1 of Compound (XI)	161 - 165
364	Cl-	$-CH_2$-	$HOCH_2(CHOH)_4CONH$-(N—N, S ring)-SNa	$HOCH_2(CHOH)_4CONH$-(N—N, S ring)-S-	"	89 - 92

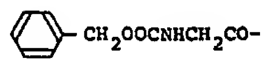
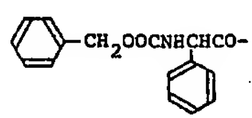
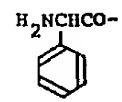
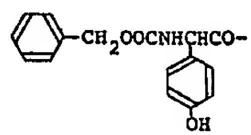
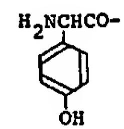
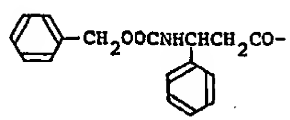
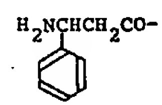
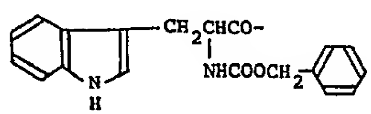
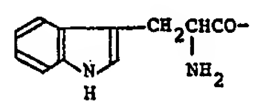
Example 365.

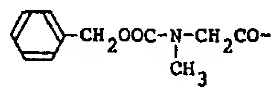
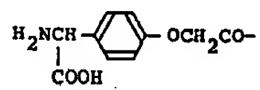
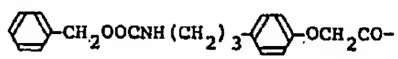
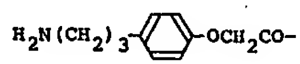
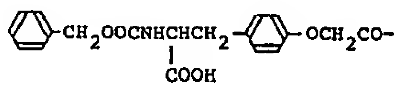
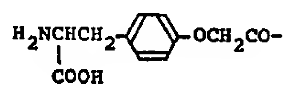
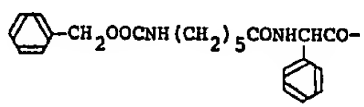
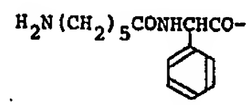
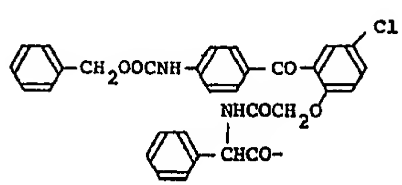
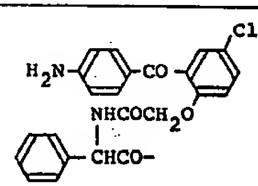
10% Palladium · carbon (25 mg) was added to a methanol solution (10 ml.) of 3-(6-benzyloxycarbonylaminohexanamido)lactacillanic acid (220 mg.), and a theoretical volume of hydrogen gas was introduced to the mixture in 2 hrs. at ordinary temperature and ordinary atmosphere. The reaction mixture was subjected to filtration, and the filtrate was concentrated under reduced pressure. The residue was pulverized with acetone, washed with acetone and subjected to filtration to give 3-(6-aminohexanamido)lactacillanic acid (100 mg.). Mp 118 to 122°C (dec.).

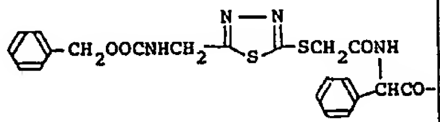
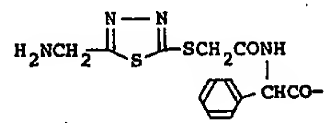
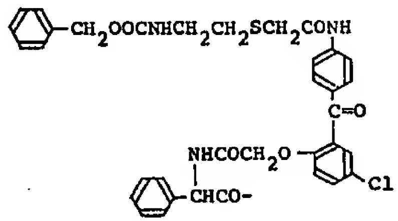
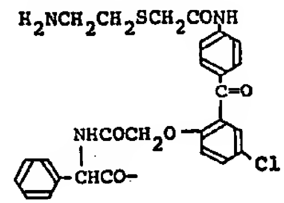
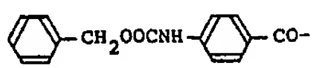
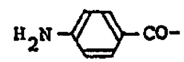
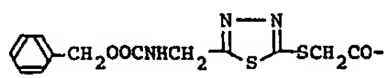
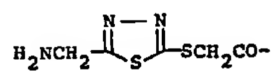
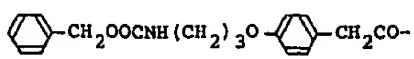
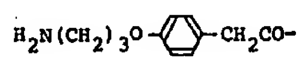
The following compounds were prepared in substantially the similar manner as described above.



(XIII) (XIV)

Example	Compound (XIII)		Compound (XIV)		
	R_{12}	R_{13}	R_{12}'	R_{13}	mp(°C) (dec.)
366		-H	H_2NCH_2CO-	the same as R_{13} of Compound (XIII)	I.R. ν cm^{-1} (Nujol): 1730, 1665, 1610
367		"		"	193 - 196
368		"		"	205 - 209
369		"		"	179 - 185
370		"		"	I.R. ν cm^{-1} (Nujol): 1730, 1660, 1600

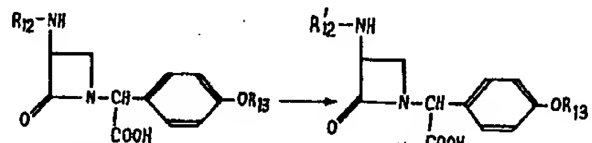
371		"	CH_3NHCH_2CO-	"	I.R. ν cm^{-1} (KBr): 1740 1660 1620
372		"		"	194 - 196
373		"		"	175 - 180
374		"		"	172 - 178
375		"		"	75 - 76
376		"		"	150 - 153

377		"		"	196 - 199
378		"		"	191 - 196
379		"		"	190 - 194
380		"		"	176 - 180
381		"	$H_2NCH_2CH_2SCH_2CO-$	"	171 - 175
382		"		"	I.R. $\nu_{cm^{-1}}$ (Nujol) 1730, 1660, 1610

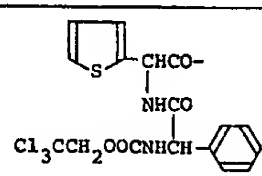
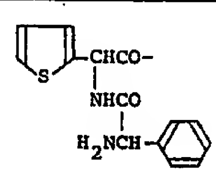
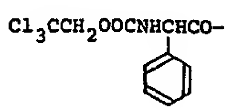
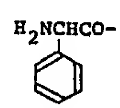
Example 383.

3 - [2 - (2 Thienyl) - N - (2,2,2 - trichloroethoxycarbonyl)glycinamido]lactacillanic acid (0.250 g.) was dissolved in a 90% acetic acid aqueous solution (13 ml.), and the solution was cooled to 10°C. To the solution, was added gradually zinc powder (1.20 g) in 50 minutes, and the mixture was subjected to reaction for an hour at the same temperature. To the reaction mixture, was added zinc powder (0.50 g.) in 30 minutes, and then the mixture was subjected to further reaction for 2 hrs. The zinc powder was removed by filtration, and hydrogen sulfide gas was introduced to the filtrate, and then the precipitate was removed by filtration. The filtrate was washed with ethyl acetate, and the remaining aqueous layer was concentrated. The residue was crystallized from a mixture of methanol and ether to give 3-[2-(2-thienyl)glycinamido]lactacillanic acid (35 mg.). Furthermore, the ethyl acetate layer was extracted with water, and the aqueous layer was concentrated to recover the same compound (15 mg.). Total yield was 50 mg. Mp 184 to 189°C (dec.).

The following compounds were prepared in substantially the similar manner as described above.



(XIII) (XIV)

Example	Compound (XIII)		Compound (XIV)		
	R_{12}	R_{13}	R_{12}'	R_{13}	mp (°C) (dec.)
384		-H		the same as R_{13} of Compound (XIII)	198 - 202
385		"		"	193 - 196

Example 386.

1 - (α - Carboxy - 3,5 - dibromo - 4 - hydroxybenzyl) - 3 - [2 - [4 - {3 - carboxy-3 - (2,2,2 - trifluoroacetamido)propoxy}phenyl] - 2 - hydroxyiminoacetamido] - 2-azetidinone (0.50 g.) was suspended in water (3 ml.), and 1N-sodium hydroxide aqueous solution (3 ml) was added to said suspension, and then the solution was stirred for 30 minutes. The reaction mixture was adjusted to pH 3 with 10% hydrochloric acid under ice-cooling. The precipitated crystals were collected by filtration, and the crystals were dissolved in a small amount of a sodium bicarbonate aqueous solution, and then the solution was treated with activated carbon. After the treatment, the solution was adjusted to pH 4 with 10% hydrochloric acid under ice-cooling, and the precipitate was collected by filtration to give 1 - (α - carboxy - 3,5 - dibromo - 4 - hydroxybenzyl) - 3 - [2 - {4 - (3 - amino - 3 - carboxypropoxy)phenyl} - 2 - hydroxyiminoacetamido] - 2 - azetidinone (40 mg.). Furthermore, the same compound (60 mg.) was recovered from the mother liquor. Total yield was 100 mg. Mp 190 to 194°C (dec.).

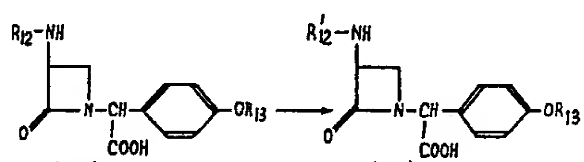
Example 387.

10% Palladium : carbon (25 mg.) was added to a methanol solution (15 ml.) of 3-[2-(4-benzyloxycarbonyloxyphenyl)acetamido]lactacillanic acid (230 mg.), and a theoretical volume of hydrogen gas was added to said mixture in 2 hrs. at ordinary temperature and ordinary atmosphere. The reaction mixture was subjected to filtration and the filtrate was concentrated under reduced pressure, and then the residue was crystallized from a mixture of acetone and ethyl acetate. The crystals were collected by filtration and washed with ethyl acetate to give 3-[2-(4-hydroxyphenyl)acetamido]lactacillanic acid (90 mg.). Mp 171 to 176°C (dec.).

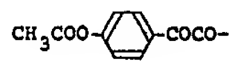
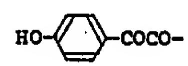
Example 388.

A solution consisting of 3-(2-ethoxycarbonyl-2-phenylacetamido)lactacillanic acid (213 mg.), ethanol (5 ml.) and 1N-sodium hydroxide aqueous solution (1.4 ml.) was subjected to reaction at ambient temperature for 1.25 hrs. After the reaction, the reaction mixture was cooled and adjusted to pH 1 by adding 1N-hydrochloric acid (1.4 ml.). Then, the mixture was adjusted to pH 6 to 7 by adding 1N-sodium hydroxide aqueous solution, and concentrated. The residue was dissolved in water, and the solution was adjusted to pH 1 to 2 with 1N-hydrochloric acid, and then washed with ethyl acetate. The remaining aqueous layer was adjusted to pH 6 with 1N-sodium hydroxide aqueous solution, and concentrated. For the purpose of isolation and purification, the residue was subjected to column chromatography using a nonionic adsorption resin, Amberlite XAD—2 (trade mark, maker; Rohm and Haas Co. Ltd.) (30 ml.) which was washed in advance with methanol and water. The fractions eluted with water were collected, and the water was distilled off from the eluate to give 3-(2-carboxy-2-phenylacetamido)lactacillanic acid, disodium salt of the carboxy group (159 mg.). Mp 209 to 214°C (dec.).

The following compounds were prepared in substantially the similar manner as described above.



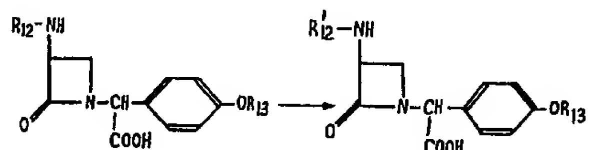
(XIII) (XIV)

Example	Compound (XIII)		Compound (XIV)		
	R_{12}	R_{13}	R_{12}'	R_{13}	mp(°C) (dec.)
389	$CH_3OOC-CH_2CH_2CO-$	-H	$NaOOC-CH_2CH_2CO-$	the same as R_{13} of Compound (XIII)	I.R. ν cm^{-1} (KBr): 1740, 1660, 1585
390		"		"	220 - 225

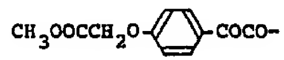
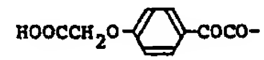
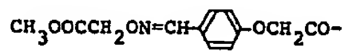
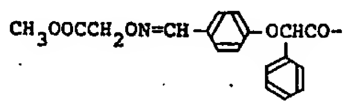
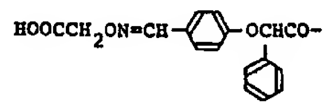
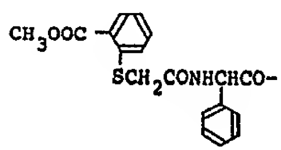
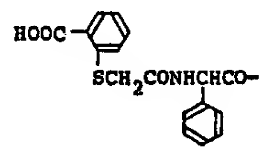
Example 391.

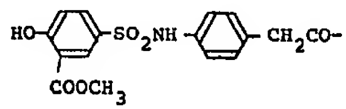
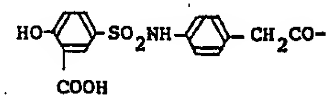
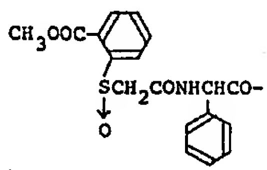
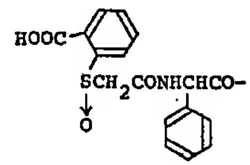
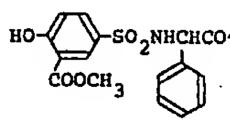
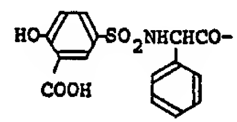
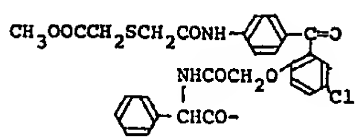
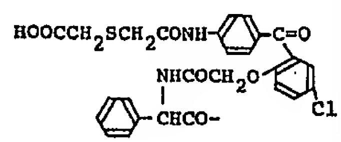
3 - [2 - {2 - (2 - Ethoxycarbonylphenoxy)acetamido} - 2 - phenylacetamido]-lactacillanic acid (17 mg.) was dissolved in 1N-sodium hydroxide aqueous solution (0.9 ml.), and the solution was stirred at ambient temperature for 3.5 hrs. Water (about 10 ml.) was added to the reaction mixture. The mixture was adjusted to pH 1 with 10% hydrochloric acid and extracted with ethyl acetate. The extract was washed twice with a sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. The solvent was distilled off from the ethyl acetate solution, and the residue was crystallized from diisopropyl ether to give 3-[2-{2-(2-carboxyphenoxy)acetamido}-2-phenylacetamido]lactacillanic acid (120 mg.). Mp 130 to 135°C (dec.).

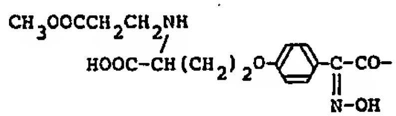
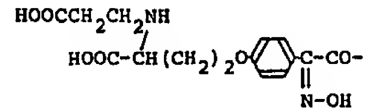
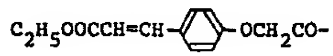
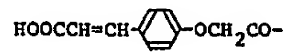
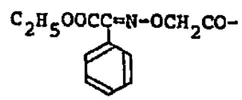
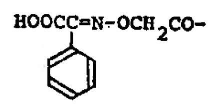
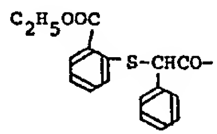
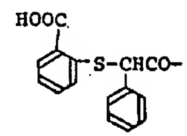
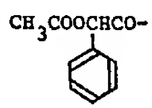
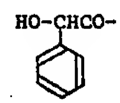
The following compounds were prepared in substantially the similar manner as described above.

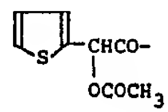
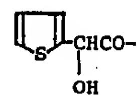
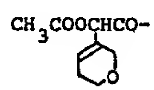
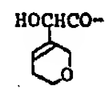
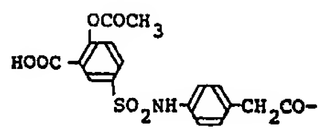
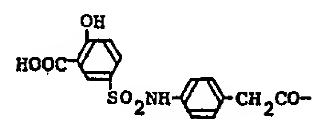
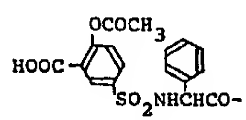
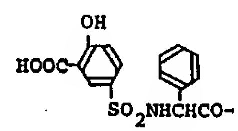
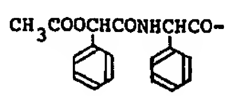
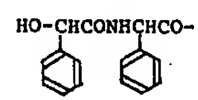


(XIII) (XIV)

Example	Compound (XIII)		Compound (XIV)		
	R_{12}	R_{13}	R_{12}'	R_{13}	mp (°C) (dec.)
392		-H		the same as R_{13} of Compound (XIII)	90 - 95
393		"		"	144 - 147
394		"		"	117 - 121
395		"		"	143 - 146

396		"		"	150 - 154
397		"		"	175 - 181
398		"		"	162 - 166
399		"		"	202 - 206

400		"		"	193 - 196
401		"		"	139 - 140
402		"		"	95 - 101
403		"		"	90 - 95
404		"		"	180 - 183

405		"		"	187 - 191
406		"		"	I.R. ν cm^{-1} (Nujol): 1740, 1685, 1660
407		"		"	150 - 154
408		"		"	162 - 166
409		"		"	90 - 93

Example 410.

1 - (α - Methoxycarbonyl - 4 - methoxybenzyl) - 3 - [2 - [4 - {3 - methoxycarbonyl - 3 - (2,2,2 - trifluoroacetamido)propoxy}phenyl] - 2 - methoxyiminoacetamido] - 2 - azetidinone (0.19 g.) was dissolved in acetone (2 ml.). 1N-Sodium hydroxide aqueous solution (0.9 ml.) was added to the solution at ambient temperature, and the mixture was stirred for 5 minutes. The acetone was distilled off from the reaction mixture, and the remaining solution was adjusted to pH 3 with 10% hydrochloric acid. The separated oily material was isolated by decantation, washed with acetone and water, and then pulverized with acetonitrile to give 1 - (α - carboxy - 4 - methoxybenzyl) - 3 - [2 - {4 - (3 - amino - 3 - carboxypropoxy)phenyl} - 2 - methoxyiminoacetamido] - 2 - azetidinone (0.02 g.). Mp 170 to 176°C (dec.).

Example 411.

3 - [2 - [4 - {4 - Chloro - N - (2,2,2 - trichloroethoxycarbonyl)anilinomethyl}-phenoxy] - 2 - methyl - propionamido]lactacillanic acid (320 mg.) was treated in substantially the similar manner as described in Example 365 to give 3 - [2 - {4 - (4-chloroanilinomethyl)phenoxy} - 2 - methylpropionamido] lactacillanic acid (110 mg.). Mp 130 to 136°C (dec.).

Example 412.

Sodium methylate (15 mg.) and absolute methanol (20 ml.) were added to 1-methoxalyl-3-(2-phenoxyacetamido)-2-azetidinone (1.1 g.), and the mixture was heated under reflux for 30 minutes. The solvent was distilled off from the reaction mixture under reduced pressure, and the residue was dissolved in acetone, and then the insoluble material was filtered off. The filtrate was concentrated and allowed to stand cool, and then the precipitated crystals were collected by filtration. The crystals were washed with acetone and dried to give 3-(2-phenoxyacetamido)-2-azetidinone (456 mg.). Furthermore, the same compound (109 mg.) was recovered from the mother liquor. Total yield was 565 mg. Mp 153 to 155°C.

Example 413.

1-Methoxalyl-3-benzyloxycarbonylamino-2-azetidinone (240 mg.) was dissolved in methanol (10 ml.), and sodium methylate (6 mg.) was added to said solution, and then the mixture was heated under reflux for 45 minutes. The methanol was distilled off from the reaction mixture, and the residue was washed with ether to give crude 3-benzyloxycarbonylamino-2-azetidinone (126 mg.). Furthermore, this product was recrystallized from acetone to give the purified compound (50 mg.). And, the purified same compound (54 mg.) was recovered from the mother liquor. Total yield was 104 mg. Mp 164 to 165°C.

Example 414.

1-(1-Acetoxy-2-methylpropyl)-3-(2-phenylacetamido)-2-azetidinone (13.8 g.) was dissolved in a solution of methanol (100 ml.) and water (100 ml.). Potassium carbonate (6 g.) and sodium borohydride (1.65 g.) were added to said solution under ice-cooling, and the mixture was subjected to reaction at 20°C for an hour. The precipitated crystals were collected by filtration, washed with water and dried to give 3-(2-phenylacetamido)-2-azetidinone (5.15 g.). Furthermore, the same compound (1.35 g.) was recovered from the filtrate. Total yield was 6.5 g. Mp 191 to 193°C.

Example 415.

1 - [1 - (2,2,2 - Trichloroethoxycarbonylamino) - 2 - methylpropyl] - 3 - (2-phenylacetamido) - 2 - azetidinone (1.13 g.) was dissolved in a 90% acetic acid aqueous solution (20 ml.), and the solution was cooled to 5°C. Zinc powder (1.62 g.) was added dropwise to said solution in 5 minutes, and the mixture was stirred for 30 minutes. Furthermore, zinc powder (1.62 g.) was added to said mixture, and the mixture was stirred for 2 days. The reaction mixture was neutralized with a sodium bicarbonate aqueous solution, and extracted with methylene chloride. The extract was washed with water and dried over anhydrous magnesium sulfate, and then the solvent was distilled off from the solution. The residue (0.65 g.) was subjected to preparative thin layer chromatography using silica : gel [developing solvent: a mixed solvent of ethyl acetate, ethyl methyl ketone, water and formic acid (volume ratio 5:3:1:1)], isolated and purified to give 3-(2-phenylacetamido)-2-azetidinone (0.3 g.). Mp 190 to 192°C.

Example 416.

1 - (α - Methoxycarbonyl - 4 - hydroxybenzyl) - 3 - [2 - (2 - thienyl)acetamido] - 2 - azetidinone (0.18 g.) was dissolved in a solution consisting of sodium borate buffer (pH 7.8) (3 ml.), methanol (5 ml.) and acetone (3 ml.), and the solution was cooled

to $-5°C$. A methanol (0.5 ml.) solution containing tert-butyl hypochlorite (0.10 g.) was added to said solution three times every 15 minutes, and the mixture was stirred for 30 minutes. The solvent was distilled off from the reaction mixture, and the remaining solution was adjusted to pH 2 with 10% hydrochloric acid, and then extracted with ethyl acetate. The extract was separated out, washed with water and a sodium chloride-saturated-aqueous solution, and dried over anhydrous magnesium sulfate. The solvent was distilled off from the ethyl acetate solution, and the residue (0.22 g.) was subjected to column chromatography using silica : gel (10 g.). The fractions eluted with chloroform were collected, and the chloroform was distilled off from the eluate to give 1 - (α - methoxycarbonyl - 3,5 - dichloro - 4 - hydroxybenzyl) - 3 - [2 - (2 - thienyl)-acetamido] - 2 - azetidinone (50 mg.).

I.R. absorption spectrum,

ν cm^{-1} (liquid film): 3270, 1760, 1755, 1665.

Example 417.

Chloroform (1.5 ml.) was added to a solution of 1-(α-methoxycarbonyl-4-hydroxybenzyl)-3-(2-phenylacetamido)-2-azetidinone (184 mg.) dissolved in dioxane (2 ml.), and a chloroform (0.5 ml.) solution containing bromine (184 mg.) was added dropwise to said mixture in 5 minutes under ice-cooling. After addition of ethyl acetate (80 ml.) to said reaction mixture, the ethyl acetate layer was separated out, washed with water and dried over anhydrous magnesium sulfate. This solution was concentrated, and the residue was dissolved in a small amount of acetone. The solution was subjected to preparative thin layer chromatography using silica : gel [developing solvent; a mixture of chloroform and methanol (5:0.3)] for isolation and purification. The product thus obtained was recrystallized from a mixture of ethyl acetate and acetone to give 1 - (α-methoxycarbonyl - 3 - bromo - 4 - hydroxybenzyl) - 3 - (2 - phenylacetamido) - 2-azetidinone (18 mg.). Mp 151 to 153°C (dec.).

Example 418.

A methanol solution (1 ml.) of bromine (352 mg.) was rapidly added dropwise to a solution (5 ml.) of 3-(2-phenylacetamido)lactacillanic acid (354 mg.) and sodium acetate (246 mg.) dissolved in absolute methanol with stirring under ice-cooling. The methanol was distilled off from the reaction mixture under reduced pressure. After addition of a mixture of ethyl acetate and water to the residue, the ethyl acetate layer was separated out and washed with water and dried over anhydrous magnesium sulfate. The solvent was distilled off from the solution, and the residue (590 mg.) as the yellow orange oily material was dissolved in a small amount of ethyl acetate, and the solution was subjected to column chromatography using silica : gel (7 g.). The fractions, eluted with a mixed solvent of ethyl acetate and acetone, were collected, and the solvent was distilled off from the eluate. The residue thus obtained was further subjected to preparative thin layer chromatography using silica : gel for isolation and purification. The fractions, eluted with a mixture of ethyl acetate and acetic acid (5:1), were collected, and the solvent was distilled off from the eluate, and then the residue was pulverized with chloroform. This powder was recrystallized from a mixture of chloroform and acetone to give 1 - (α - carboxy - 3,5 - dibromo - 4 - hydroxybenzyl) - 3 - (2-phenylacetamido) - 2 - azetidinone (157 mg.). Furthermore, the same compound (26 mg.) was recovered from the mother liquor. Total yield was 183 mg. Mp 161 to 162°C (dec.).

Example 419.

3 - [2 - [4 - {3 - Carboxy - 3 - (2,2,2 - trifluoroacetamido)propoxy}phenyl] - 2-hydroxyiminoacetamido]lactacillanic acid (1.77 g.) was dissolved in methanol (20 ml.). After addition of sodium acetate (1.03 g.) to said solution, the mixture was cooled to $-5°C$ and a methanol solution (5 ml.) of bromine (1.06 g.) was added dropwise thereto in 15 minutes. The reaction mixture was subjected to reaction for 15 minutes, and the methanol was distilled off from the reaction mixture, and then the residue was added to a mixture of ethyl acetate (20 ml.) and water (20 ml.). After adjusting the mixture to pH2 with 2% hydrochloric acid, the ethyl acetate layer was separated out and washed with a sodium thiosulfate aqueous solution, water and a sodium chloride-saturated-aqueous solution respectively, and then dried over anhydrous magnesium sulfate. The ethyl acetate solution was concentrated, and the residue (2.56 g.) thus obtained was subjected to precipitation repeatedly twice with a mixture of benzene and acetone to give 1 - (α - carboxy - 3,5 - dibromo - 4 - hydroxybenzyl) - 3 - [2 - [4-{3 - carboxy - 3 - (2,2,2 - trifluoroacetamido)propoxy}phenyl] - 2 - hydroxyimino-acetamido] - 2 - azetidinone (1.16 g.).

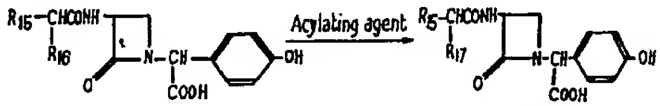
I.R. absorption spectrum:

ν cm^{-1} (liquid film): 1720 (broad), 1650.

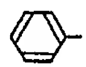
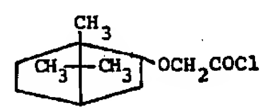
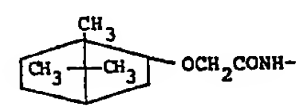
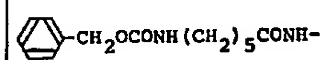
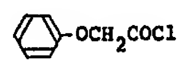
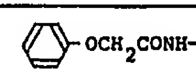
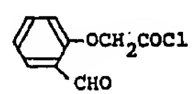
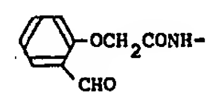
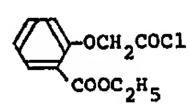
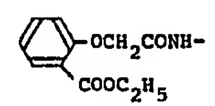
Example 420.

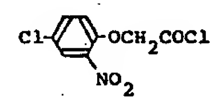
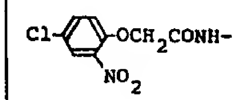
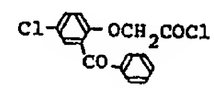
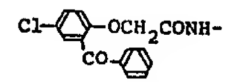
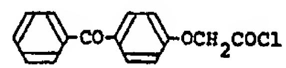
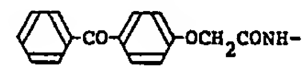
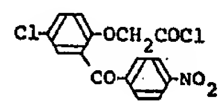
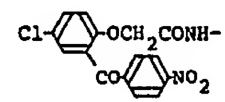
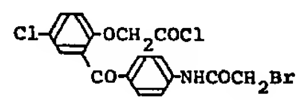
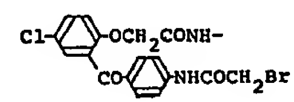
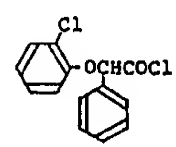
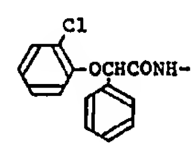
3-Glycinamidolactacillanic acid (100 mg.) suspended in water (5 ml.) was dissolved by adding sodium bicarbonate (70 mg.). The solution was cooled to 0 to 5°C, and a solution of 2-(4-chloro-2-nirtophenoxy)acetyl chloride (100 mg.) dissolved in acetone (5 ml.) was added dropwise thereto. The mixture was allowed to react at the same temperature for 2 hrs. The acetone was distilled off from the reaction mixture under reduced pressure, and the remaining solution was adjusted to pH 1 to 2 by adding diluted hydrochloric acid and then extracted with ethyl acetate. The extract was washed with water and dried, and the solvent was distilled off. The oily residue was washed wih ether, dissolved in a small amount of methanol, and then ether was added to the solution. The precipitated powder was collected by filtration and dried to give 3 - [2 - {2 - (4 - chloro - 2 - nitrophenoxy)acetamido}acetamido] - lactacillanic acid (82 mg.). Mp 149 to 153°C (dec.).

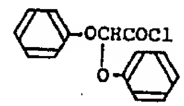
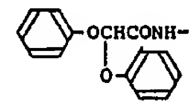
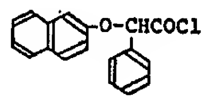
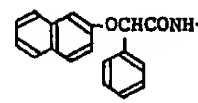
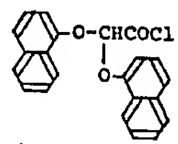
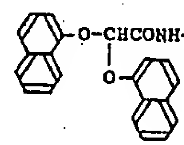
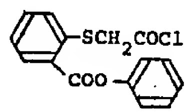
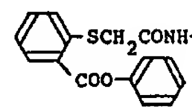
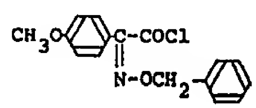
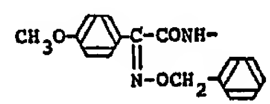
The following compounds were prepared in substantially the similar manner as described above.

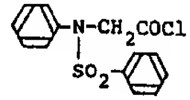
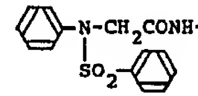
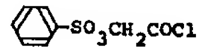
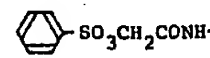
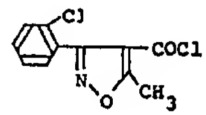
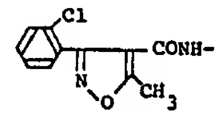
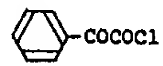
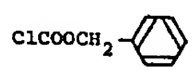
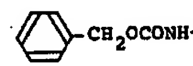


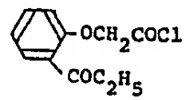
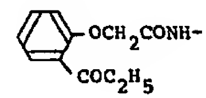
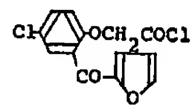
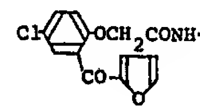
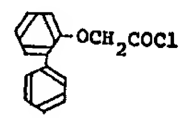
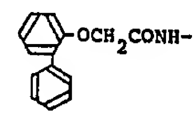
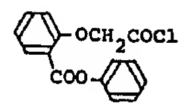
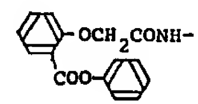
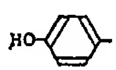
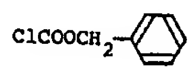
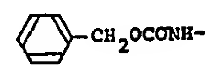
(XVII) (XVIII)

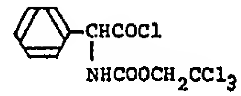
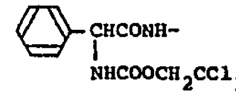
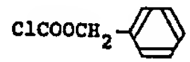
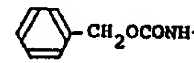
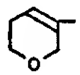
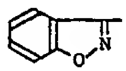
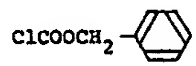
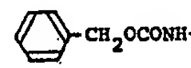
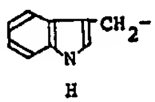
Example	Compound (XVII)		Acylating agent	Compound (XVIII)		
	R_{15}	R_{16}		R_{15}	R_{17}	mp(°C) (dec.)
421		H_2N-	$BrCH_2COCl$	the same as R_{15} of the Compound (XVII)	$BrCH_2CONH$-	156 - 161
422	"	"		"		130 - 134
423	"	"		"		111 - 116
424	"	"		"		107 - 111
425	"	"		"		191 - 195
426	"	"		"		127 - 130

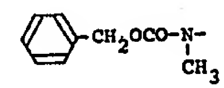
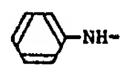
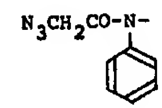
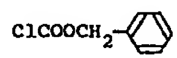
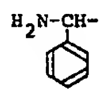
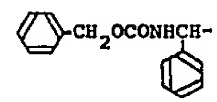
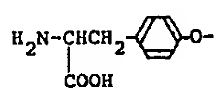
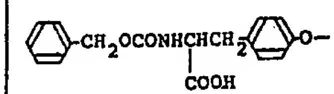
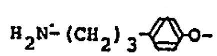
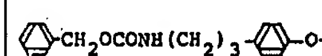
427	"	"		"		77 - 81
428	"	"		"		135 - 137
429	"	"		"		154 - 159
430	"	"		"		148 - 153
431	"	"		"		158 - 162
432	"	"		"		112 - 116

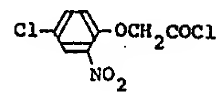
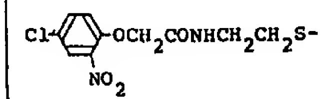
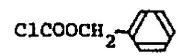
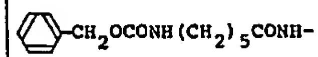
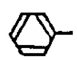
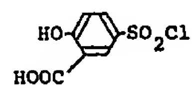
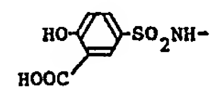
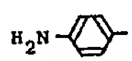
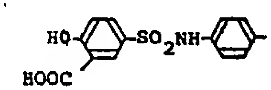
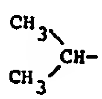
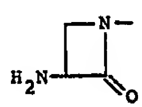
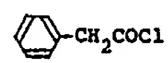
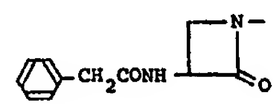
433	"	"		"		102 - 105
434	"	"		"		158 - 161
435	"	"		"		135 - 139
436	"	"		"		141 - 146
437	"	"		"		118 - 121

438	"	"		"		137 - 142
439	"	"		"		151 - 155
440	"	"		"		122 - 124
441	"	"		"		143 - 146
442	"	"	C_2H_5O-COCOCl	"	C_2H_5O-COCONH-	118 - 123
443	"	"		"		146 - 148
444	"	"	$ClCOOCH_2CCl_3$	"	Cl_3CCH_2OCONH-	130 - 132

445	"	"		"		125 - 130
446	"	"		"		141 - 144
447	"	"		"		125 - 130
448	"	"		"		143 - 148
449		"		"		I.R. $\nu\,cm^{-1}$ (Nujol): 1760, 1730, 1680
450		"	$BrCH_2COCl$	"	$BrCH_2CONH-$	147 - 150

451	"	"		"		165 - 169
452	"	"		"		I.R. ν cm^{-1} (liquid film): 1730, 1710, 1650
453	"	"	ClCOOCH$_2$CCl$_3$	"	Cl$_3$CCH$_2$OCONH-	171 - 176
454		"	ClCH$_2$COCl	"	ClCH$_2$CONH-	211 - 217
455		"		"		165 - 168
456		"	"	"	"	235 - 240

457	H-	CH_3NH-	"	"		I.R. ν cm^{-1} (liquid film): 1740, 1710 1690, 1650
458	"		N_3CH_2COCl	"		176 – 180
459	"	$H_2N-(CH_2)_4-$		"		I.R. ν cm^{-1} (Nujol): 1730, 1660
460	"		"	"		169 – 173
461	"		"	"		125 – 130
462	"		"	"		142 – 146

463		$H_2N-CH_2CH_2S-$		"		77 - 81
464	"	$H_2N-(CH_2)_5CONH-$		"		111 - 116
465	H-	H_2N-		"		168 - 173
466		"		"		162 - 166
467	H-		-	"		150 - 154
468				"		160 - 164

Example 469.

3-(2-Phenylglycinamido)lactacillanic acid as a starting material and 2-[4-chloro-2-(α-acetoxyiminobenzyl)phenoxy]acetyl chloride as an acylating agent were treated in substantially the similar manner as described in Example 420 to give 3-[2-[2-{4-chloro-2-(α-hydroxyiminobenzyl)phenoxy}acetamido]-2-phenylacetamido]lactacillanic acid, in which the protective group (i.e. acetyl) on the hydroxyimino group of the starting material was eliminated. Mp 171 to 176°C (dec.).

Example 470.

A suspension of 3-(2-Phenylglycinamido)lactacillanic acid (200 mg.) in a solution consisting of methylene chloride (10 ml.), N,N-dimethylformamide (1 ml.) and N,O-bis(trimethylsilyl)acetamide (1 ml.), was stirred at ambient temperature for an hour. 2-Anilino-2-phenylacetyl chloride hydrochloride (140 mg.) was added to the reaction mixture under ice-cooling, and the mixture was stirred at the same temperature for an hour for dissolution. Furthermore, the reaction mixture was stirred at ambient temperature for an hour and then concentrated under reduced pressure. After addition of ethyl acetate and water to the residue, the ethyl acetate layer was separated out and extracted with a sodium bicarbonate aqueous solution. After adjusting the aqueous layer to pH 1 to 2 with 1N-hydrochloric acid, it was extracted with ethyl acetate and the extract thus obtained was washed with water and dried over anhydrous magnesium sulfate. After solvent was distilled off, ether was added to the residue thus obtained and then the mixture was stirred for an hour. The separated powder was collected by filtration to give 3 - [2 - phenyl - 2 - (2 - anilino - 2 - phenylacetamido)acetamido]lactacillanic acid (89 mg.). Mp 158 to 161°C (dec.).

Example 471.

A mixture of N,N-dimethylformamide (50 mg.) and thionyl chloride (200 mg.) was stirred at 40 to 50°C. for 30 minutes. After the excess of the thionyl chloride was distilled off, the residue was dissolved in methylene chloride (5 ml.), and then the solution was cooled to −10 to −5°C. 2-[5-(2-Thienyl)tetrazol-1-yl]acetic acid (114 mg.) was added to this solution at once and dissolved by adding N,N-dimethylformamide (2 drops), and then the mixture was stirred for 15 minutes. This solution was cooled to −60 to −50°C, and a methylene chloride (2 ml.) solution of triethylamine (65 mg.) was added thereto, and then the mixture was stirred at the same temperature for 30 minutes. To the solution cooled to −60 to −50°C, there was added at once a solution which had been prepared in advance by stirring a suspension consisting of 3-(2-phenylglycinamido)lactacillanic acid (200 mg.), N,O-bis(trimethylsilyl)acetamide (430 mg.), methylene chloride (10 ml.) and N,N-dimethylformamide (1 ml.) at the same temperature for an hour. The reaction mixture was stirred for 30 minutes at the same temperature and for an hour at −20 to −10°C and further for an hour at −10 to 0°C. The solvent was distilled off from the reaction mixture to leave the residue, to which ethyl acetate and a sodium bicarbonate aqueous solution were added. The aqueous layer was separated out, adjusted to pH 4 with 10% hydrochloric acid and then extracted with ethyl acetate. The ethyl acetate layer was separated out, washed with water, dried over anhydrous magnesium sulfate and then the solvent was distilled off. The residue (70 mg.) thus obtained was washed with ether to give crude 3-[2-phenyl-2-[2-{5-(2-thienyl)tetrazol-1-yl}acetamido]acetamido]lactacillanic acid (60 mg.). Furthermore, the product was dissolved in ethyl acetate, and ether was added to the solution to precipitate crystals. The crystals were collected by filtration to give the purified product (30 mg.). Mp 170 to 174°C (dec.).

Example 472.

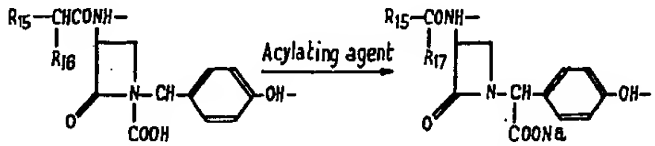
2-Phenylglycolic acid, instead of the 2-[5-(2-thienyl)tetrazol-1-yl]acetic acid, was treated in substantially the similar manner as described in Example 471 to give 3-[2-(2-hydroxy-2-phenylacetamido)-2-phenylacetamido]lactacillanic acid. Mp 90 to 93°C (dec.).

Example 473.

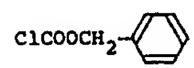
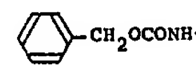
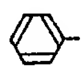
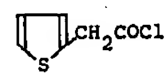
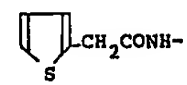
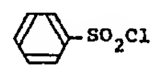
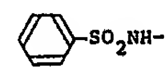
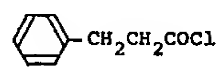
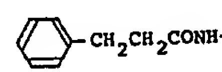
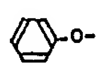
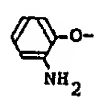
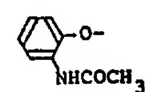
Acetone (5 ml.) was added to an aqueous solution (5 ml.) of 3-[2-(2-thienyl)-glycinamido]lactacillanic acid (0.358 g.) and sodium bicarbonate (0.185 g.), and the solution was cooled to 0 to 5°C. To the solution, there was added dropwise a dried acetone (5 ml.) solution of 2-(4-chloro-2-nitrophenoxy)acetyl chloride (0.230 g.), and the mixture was allowed to react at the same temperature for 2 hrs. After the acetone was distilled off from the reaction mixture under reduced pressure, the remaining aqueous layer was washed with ethyl acetate, adjusted to pH 1 to 2 with diluted hydrochloric acid and then extracted with ethyl acetate. The extract was washed with water

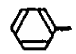
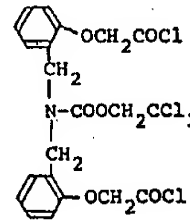
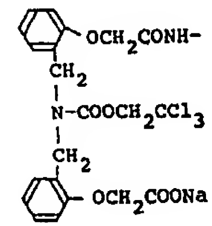
and dried, and the solvent was distilled off to give the residue (0.34 g.). The residue was dissolved in methanol (2 ml.), and to the solution, there was added an acetone (1 ml.) solution of sodium 2-ethylhexanate (0.88 g.) and then ether (15 ml.). The precipitated powder was collected and washed three times with ether to give sodium salt of 3 - [2 - {2 - (4 - chloro - 2 - nitrophenoxy)acetamido} - 2 - (2 - thienyl)acetamido]lactacillanic acid (0.140 g.). Mp 187 to 190°C (dec.).

The following compounds were prepared in substantially the similar manner as described above.



(XVII) (XVIII)

Example	Compound (XVII)		Acylating agent	Compound (XVIII)		
	R_{15}	R_{16}		R_{15}	R_{17}	mp(°C) (dec.)
474	H-	H_2N-		the same as R_{15} of the Compound (XVII)		I.R. ν cm^{-1} (Nujol): 1740, 1675, 1610
475	"	"	CH_3SO_2Cl	"	CH_3SO_2NH-	160 - 164
476		"		"		221 - 224
477	"	"		"		186 - 189
478		"		"		224 - 227
479			CH_3COCl	"		192 - 197

480		H_2N-		"		181 - 187

Example 481.

Sodium nitrite (140 mg.) was little by little added to a solution of guanidinocarbohydrazide dihydrochloride (380 mg.) dissolved in water (3 ml.) under cooling at 0 to 5°C, and the mixture was stirred for 10 minutes to provide a solution of guanidinocarbonylazide. On the other hand, 3-(2-phenylglycinamido)lactacillanic acid (220 mg.) and sodium bicarbonate (150 mg.) were dissolved in a mixture of water (8 ml.) and acetone (4 ml.), and the solution was stirred at 0 to 5°C for 15 minutes. After removal of the insoluble material by filtration from said solution, the solution as prepared above was added dropwise to the filtrate in 5 minutes and then the mixture was stirred at 0 to 5°C for 2 hrs, while the reaction mixture was kept at pH 7.5 to 8.0 by adding 5% sodium bicarbonate aqueous solution. The precipitated crystals in the reaction mixture were collected by filtration to give 3-(2-guanidinocarbonylamino-2-phenylacetamido)-lactacillanic acid (20 mg.). Furthermore, the filtrate was concentrated to a volume of about 5 ml. to precipitate crystals, which were collected by filtration to recover the same compound (60 mg.). Total yield was 80 mg. Mp 198 to 202°C (dec.).

Example 482.

3-[2-(2-Thienyl)glycinamido]lactacillanic acid (375 mg.) suspended in water (5 ml.) was dissolved by adding potassium carbonate (104 mg.) (the nature of the solution indicated about pH 9). To said solution, there was added a solution (10 ml.) of acetone and water (1:1) and then was added dropwise a dried acetone (5 ml.) solution of benzoyl isothiocyanate (163 mg.) with stirring at ambient temperature. The mixture was stirred for 3 hrs. (during that time, the reaction mixture was kept at pH 8.5 by adding a solution of potassium carbonate (104 mg.) in water (7 ml.)). The acetone was distilled off from the reaction mixture. The aqueous residue was washed

with ethyl acetate, adjusted to pH 1 to 2 with diluted hydrochloric acid and extracted with ethyl acetate. The extract was washed with water and dried, and the solvent was distilled off. The oily residue (469 mg.) was chromatographed on silica gel (7 g.) and eluted with a mixture of ethyl acetate and methanol to give 3-[2-(3-benzoylthioureido)-2-(2-thienyl)acetamido]lactacillanic acid (97 mg.) Mp 124 to 129°C (dec.).

Example 483.

85% 3-Chloroperbenzoic acid (50 mg.) was added to a solution of 3-(2-methylthio-2-phenylacetamido)lactacillanic acid (100 mg.) dissolved in methanol (5 ml.) under ice-cooling, and the mixture was allowed to react with stirring at the same temperature for an hour. The reaction mixture was concentrated under reduced pressure, and the residue was washed with chloroform to give 3-(2-methylsulfinyl-2-phenylacetamido)lactacillanic acid (86 mg.).

I.R. absorption spectrum,

ν cm^{-1} (Nujol: 1740, 1720, 1665, 1020.

Example 484.

85% Chloroperbenzoic acid (61 mg.) was added to a solution of 3-[2-{N-(2-naphthyl)carbamoylmethylthio}-2-phenylacetamido]lactacillanic acid (171 mg.) dissolved in acetone (7 ml.) under ice-cooling, and the mixture was allowed to react with stirring at the same temperature for an hour. The reaction mixture was concentrated, and the residue was crystallized from chloroform to give 3-[2-{N-(2-naphthyl)carbamoylmethylsulfinyl}-2-phenylacetamido]lactacillanic acid (134 mg.). Mp 151 to 155°C (dec.).

Example 485.

3 - [2 - {4 - (3 -Amino - 3 - carboxypropoxy)phenyl}glycinamido]lactacillanic acid. (1.00 g.) was dissolved in an aqueous solution (20 ml.) of sodium bicarbonate (0.66 g.), and acetone (10 ml.) was added thereto. After the solution was ice-cooled, an acetone solution (5 ml.) of 2,4-dinitro-1-fluorobenzene (0.75 g.) was added dropwise thereto with stirring, and then the mixture was stirred at the same temperature for 30 minutes and further at ambient temperature for 5 hours. The reaction mixture was washed with ethyl acetate and was adjusted to pH 2 with 10% hydrochloric acid, and then extracted with ethyl acetate. The ethyl acetate layer was separated, and the solvent was distilled off under reduced pressure. The residue was pulverized with ether to give 3 - [2 - [4 - {3 - carboxy - 3 - (2,4 - dinitroanilino)propoxy}phenyl] - 2 - (2,4-dinitroanilino)acetamido]lactacillanic acid (1.50 g.).

I.R. absorption spectrum,

ν cm^{-1} (Nujol): 1735, 1700 (shoulder), 1520, 1340.

Example 486.

3 - [2 - {4 - (3 - Amino - 3 - carboxypropoxy)phenyl} - glycinamido]lactacillanic acid (0.49 g.) and sodium bicarbonate (0.49 g.) were dissolved in water (10 ml.), and methanol (5 ml.) was added to the solution. To the solution, there was added dropwise a methanol solution (7 ml.) of methyl 4-fluoro-3-nitrobenzoate (0.80 g.), and the mixture was allowed to react at ambient temperature for 17 hrs. and further at 50°C for 4 hours. After cooling the reaction mixture for a while, the precipitate was removed by filtration. The methanol was distilled off from the filtrate under reduced pressure, and the aqueous residue was washed with ether, adjusted to pH 3 with 1N-hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was separated and dried over anhydrous magnesium sulfate, and then the solvent was distilled off under reduced pressure. The residue was pulverized with benzene to give 3 - [2 - [4 - {3 - carboxy-3 - (4 - methoxycarbonyl - 2 - nitroanilino)propoxy}phenyl] - 2 - (4 - methoxycarbonyl - 2 - nitroanilino)acetamido]lactacillanic acid (0.86 g.). Mp 150 to 155°C (dec.).

Example 487.

3 - [2 - {4 - (3 - Benzamido - 3 - carboxypropoxy)phenyl}glycinamido]lactacillanic acid (8.9 g.) and sodium bicarbonate (5.4 g.) was dissolved in water (100 ml.), and methanol (100 ml.) and methyl 4-fluoro-3-nitrobenzoate (4.5 g.) was added thereto. The mixture was allowed to react with stirring at 40 to 50°C for 4 hrs. The methanol was distilled off from the reaction mixture under reduced pressure, and the residue was washed with ethyl acetate, adjusted to pH 2 with 10% hydrochloric acid and extracted with ethyl acetate. The extract was washed with diluted hydrochloric acid and water, and dried. The solvent was distilled off from the ethyl acetate layer under reduced pressure, and the residue was pulverized with ether and collected by filtration to give

3 - [2 - {4 - (3 - benzamido - 3 - carboxypropoxy)phenyl} - 2 - (4 - methoxycarbonyl-2 - nitroanilino)acetamido]lactacillanic acid (9.23 g.).

I.R. absorption spectrum,

ν cm^{-1} (Nujol): 1730, 1620, 1528, 1532.

Example 488.

3 - [2 - {4 - (3 - Carboxy - 3 - phthalimidopropoxy)phenyl}glycinamido]lactacillanic acid (0.68 g.) was dissolved in an aqueous solution (10 ml.) of sodium bicarbonate (0.40 g.). To the solution, there was added methanol (10 ml.) and then methyl 4-fluoro-3-nitrobenzoate (0.30 g), and the mixture was allowed to react at 50°C under stirring for 3 hrs. The methanol was distilled off from the reaction mixture, and the aqueous residue was washed with ethyl acetate, adjusted to pH 2 with 10% hydrochloric acid and then extracted with ethyl acetate. The ethyl acetate layer was separated and dried over anhydrous magnesium sulfate. The solvent was distilled off from the ethyl acetate layer under reduced pressure, and the residue was pulverized with ether to give 3 - [2 - {4 - (3 - carboxy - 3 - phthalimidopropoxy)phenyl} - 2 - (4 - methoxycarbonyl - 2 - nitroanilino)acetamido]lactacillanic acid (0.53 g.). Mp 155 to 160°C (dec.).

Example 489.

Sodium salt of 3-[2-{4-(3-amino-3-carboxypropoxy)phenyl}-2-hydroxyiminoacetamido]lactacillanic acid (0.50 g.) was dissolved in water (10 ml.). Acetone (2 ml.) was added to the solution, and after stirring the solution for a while sodium borohydride (0.30 g.) was added little by little thereto, and then the mixture was stirred for 3 hrs. Acetone (2 ml.) was added to the reaction mixture, and the solution was adjusted to pH 3 with 10% hydrochloric acid. The precipitated crystals were collected by filtration to give 3 - [2 - [4 - {3 - carboxy - 3 - (N - isopropylamino)propoxy}phenyl] - 2-hydroxyiminoacetamido]lactacillanic acid (0.05 g.). Furthermore, the mother liquor was concentrated to nearly half of its original volume, and the precipitated crystals were collected by filtration to recover the same product (0.17 g.). Total yield was 0.22 g. Mp 193 to 194°C (dec.).

Example 490.

3 - [2 - {4 - (3 - Amino - 3 - carboxypropoxy)phenyl} - 2 - hydroxyiminoacetamido]lactacillanic acid as a starting material and methyl 2-formylacetate as a carbonyl compound were treated in substantially the similar manner as described in Example 489 to give 3 - [2 - [4 - (3 - carboxy - 3 - {N - (2 - methoxycarbonylethyl)amino}propoxy]phenyl] - 2 - hydroxyiminoacetamido]lactacillanic acid. Mp 175 to 179°C (dec.).

Example 491.

Sodium salt of 3-[2-{4-(3-amino-3-carboxypropoxy)phenyl}-2-hydroxyiminoacetamido]lactacillanic acid (0.50 g.) was dissolved in water (10 ml.), 30% formaldehyde aqueous solution (1 ml.) was added thereto under ice-cooling. The mixture was stirred for a while, and sodium borohydride (0.15 g.) was added gradually thereto. After stirring the mixture for 30 minutes, it was adjusted to pH 3 with 10% hydrochloric acid under ice-cooling. The precipitated crystals were collected by filtration, washed with water and acetone, and dried at 40°C under reduced pressure to give 3 - [2 - [4 - {3-carboxy - 3 - (N,N - dimethylamino)propoxy}phenyl] - 2 - hydroxyiminoacetamido]-lactacillanic acid (0.28 g.). Mp 193 to 194°C (dec.).

Example 492.

3-(4-Nitrobenzamido)lactacillanic acid (235 mg.) was dissolved in methanol (20 ml.), and palladium : carbon (40 mg.) as a catalyst was added thereto. The mixture was shaken in a stream of hydrogen at ambient temperature under ordinary atmosphere, while a calculated volume (44 ml.) of hydrogen was absorbed in about an hour. The catalyst was removed by filtration from the reaction mixture, and the filtrate was evaporated to dryness under reduced pressure. The residue was treated with ether and collected by filtration to give 3-(4-aminobenzamido)lactacillanic acid (200 mg.). Mp 190 to 194°C (dec.).

Example 493.

3-(3 : 5-Dinitrobenzamido)lactacillanic acid (210 mg.) was dissolved in methanol (20 ml.), and palladium : carbon (40 mg.) as a catalyst was added thereto. The mixture was shaken in a stream of hydrogen at ambient temperature under ordinary atmosphere, while a calculated volume (70 ml.) of hydrogen was absorbed in 2 hrs. The catalyst was removed by filtration from the reaction mixture, and the filtrate was evaporated to dryness under reduced pressure. The residue was washed with ether and dissolved in acetone. After the acetone solution was filtered, ethyl acetate was added to

the filtrate, and then the solution was concentrated. The concentrate was filtered, and the filtrate was evaporated to dryness under reduced pressure. The residue was treated with ether and collected by filtration to give 3-(3,5-diaminobenzamido)lactacillanic acid (60 mg.). Mp 116 to 121°C (dec.).

Example 494.

3-[2-(4-Formylphenoxy)acetamido]lactacillanic acid (200 mg.) was added to a solution of hydroxylamine hydrochloride (70 mg.) dissolved in water (1 ml.) and 1N-sodium hydroxide aqueous solution (1.5 ml.), and the mixture was stirred at ambient temperature for 30 minutes. Ethyl acetate was added to the reaction mixture and 1N-hydrochloric acid (1.5 ml.) was added thereto. The mixture was shaken and the ethyl acetate layer was separated. The layer was washed with water and dried over anhydrous magnesium sulfate, and then the solvent was distilled off. The residue (190 mg.) was allowed to crystallize. A mixed solvent of ethyl acetate and chloroform (1:1) was added to the residue to precipitate crystals, and the solution was stirred at ambient temperature for an hour. The crystals were collected by filtration to give 3-[2-(4-hydroxyiminomethylphenoxy)acetamido]lactacillanic acid (130 mg.). Mp 150 to 155°C (dec.).

Example 495.

3-[2-(4-Formylphenoxy)acetamido]lactacillanic acid (200 mg.) was added to a solution consisting of 2-aminooxyacetic acid : 1/2 hydrochloride (66 mg.) and 1N-sodium hydroxide aqueous solution (1.5 ml.), and the mixture was stirred at ambient temperature for 2 hrs. The reaction mixture was adjusted to pH 2 with 1N-hydrochloric acid, and then extracted with ethyl acetate. The ethyl acetate layer was separated, washed with water and dried over anhydrous magnesium sulfate. After the solvent was distilled off from the extract, ether was added to the residue and then the mixture was stirred at ambient temperature for 2 hrs. The precipitated crystals were collected by filtration, and the crystals (150 mg.) was washed with ethyl acetate to give 3-[2-(4-carboxymethoxyiminomethylphenoxy)acetamido]lactacillanic acid (110 mg.). Mp 144 to 147°C (dec.).

Example 496.

3-[2-(4-Formylphenoxy)-2-phenylacetamido]lactacillanic acid (237 mg.) was added to a solution consisting of 2-aminooxyacetic acid : 1/2 hydrochloride (106 mg.) and 1N-sodium hydroxide aqueous solution (1.8 ml.), and the mixture was stirred at ambient temperature for 2 hrs. The reaction mixture was adjusted to pH 1 to 2 with 10% hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was separated, washed with water and dried over anhydrous magnesium sulfate. After the solvent was distilled off from the extract, the residue was washed with diisopropyl ether and collected by filtration to give 3-[2-(4-carboxymethoxyiminomethylphenoxy)-2-phenylacetamido]lactacillanic acid (190 mg.). Mp 117 to 121°C (dec.).

Example 497.

3-[2-(4-Formylphenoxy)acetamido]lactacillanic acid (200 mg.) was added to a solution of 1N-sodium hydroxide aqueous solution (5 ml.) and N-(carbazoylmethyl)-N,N,N-trimethylammonium chloride (90 mg.), and the mixture was stirred at ambient temperature for 2 hrs. Further, N-(carbazoylmethyl)-N,N,N-trimethylammonium chloride (90 mg.) was added to this solution, and the mixture was allowed to stand overnight. To the reaction mixture, there were added 1N-hydrochloric acid (0.5 ml.) and acetic acid (100 mg.), and then the solution was washed with ethyl acetate and ether. The aqueous layer was separated, and the organic solvent saturated in the layer was completely distilled off under reduced pressure. The residue was chromatographed on a nonionic adsorption resin, Amberlite XAD—2 (50 ml.) (trade mark, maker; Rohm and Haas Co., Ltd.). Elution was conducted with water and then methanol, and the fractions containing an objective compound, which can be eluted with methanol, were collected. The fractions combined together was concentrated. The residue was washed with ethanol and collected by filtration to give N - [3 - [4 - [N - { - ($\tilde{\alpha}$ - carboxy - 4 - hydroxybenzyl) - 2 - oxo - 3 - azetidinyl}carbamoylmethoxy]benzylidene]-carbazoylmethyl] - N,N,N - trimethylammonium chloride (188 mg.). Mp 199 to 205°C (dec.).

Example 498.

A solution of hydroxylamine hydrochloride (35 mg.) in water was added to 0.1N-sodium hydroxide aqueous solution (5 ml.) of 3-[2-{2-(2-benzoyl-4-chlorophenoxy)-acetamido} - 2 - phenylacetamido]lactacillanic acid (160 mg.). The solution was adjusted to pH 6.0 to 6.2 by adding a small amount of hydroxylamine hydrochloride and stirred for 10 minutes. Methanol (5 ml.) was added to the mixture, and the reaction solution, after stirred at ambient temperature for 3 hrs. was allowed to stand overnight in a refrigerator. The precipitated crystals were collected by filtration to give

3 - [2 - [2 - {4 - chloro - 2 - (α - hydroxyiminobenzyl)phenoxy}acetamido] - 2-phenylacetamido]lactacillanic acid (100 mg.). Mp to 171 to 176°C (dec.).

Example 499.

3 - [2 - {4 - (3 - Acetamido - 3 - carboxypropoxy)phenyl}glycinamido]lactacillanic acid (1.3 g.) was dissolved in 50% pyridine aqueous solution (26 ml.), and the solution was adjusted to pH 8.4 with 1N-sodium hydroxide aqueous solution. Phenyl isothiocyanate (0.40 g.) was added to the solution under ice-cooling, and the mixture was stirred for 4.5 hrs. The reaction mixture was washed with ether, and the separated aqueous layer was adjusted to pH 2 with 10% hydrochloric acid to give precipitates, which were collected by filtration. The precipitates were dissolved in a sodium bicarbonate aqueous solution, and the solution was adjusted to pH 2 with 10% hydrochloric acid. The precipitated crystals were collected by filtration to give 3 - [2 - {4 - (3-acetamido - 3 - carboxypropoxy)phenyl} - 2 - (3 - phenylthioureido)acetamido]lactacillanic acid (0.92 g.). Mp 150 to 156°C (dec.).

Example 500.

3 - [2 - {4 - (3 - Acetamido - 3 - carboxypropoxy)phenyl}glycinamido]lactacillanic acid (2.0 g.) was dissolved in 50% pyridine aqueous solution (20 ml.), and the solution was adjusted to pH 8.6 with 1N-sodium hydroxide aqueous solution under ice-cooling. 1-Naphthyl isothiocyanate (0.74 g.) was added to said solution at the same temperature, and the mixture was stirred at ambient temperature for 4 hrs. The reaction mixture was washed with ether, and the separated aqueous layer was adjusted to pH 2 with 10% phosphoric acid under ice-cooling. The precipitated solid material was collected by filtration, washed with water and then dissolved in a sodium bicarbonate-saturated-aqueous solution. The solution was adjusted to pH 2 with 10% phosphoric acid, and then the precipitated crystals were collected by filtration to give 3 - [2 - {4-(3 - acetamido - 3 - carboxypropoxy)phenyl} - 2 - {3 - (1 - naphthyl)thioureido}-acetamido]lactacillanic acid (2.5 g.). Mp 142 to 147°C (dec.).

Example 501.

3 - [2 - {4 - (3 - Acetamido - 3 - carboxypropoxy)phenyl}glycinamido]lactacillanic acid as a starting material and acetyl chloride as an acylating agent were treated in substantially the similar manner as described in Example 500 to give 3-[2-{4-(3-acetamido-3-carboxypropoxy)phenyl}-2-acetamidoacetamido]lactacillanic acid.

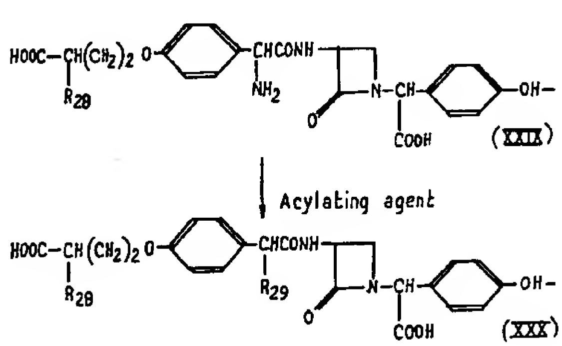
I.R. absorption spectrum,

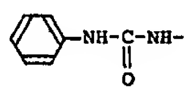
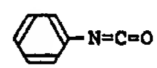
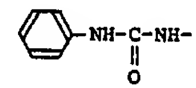
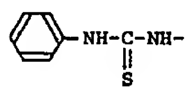
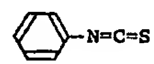
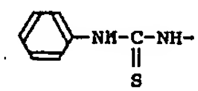
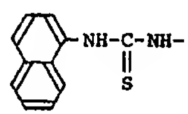
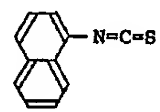
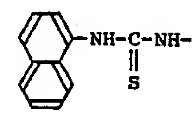
ν cm^{-1} (Nujol): 1735, 1650.

Example 502.

3 - [2 - {4 - (3 - Benzamido - 3 - carboxypropoxy)phenyl}glycinamido]lactacillanic acid (7.8 g.) was dissolved in 50% pyridine aqueous solution (160 ml.), and the solution was adjusted to pH 8.6 by adding 1N-sodium hydroxide aqueous solution. Phenyl isothiocyanate (2.64 g.) was added to said solution at the same temperature, and the mixture was stirred for 3 hrs. The reaction mixture was washed with ether, and the separted aqueous layer was adjusted to pH 2 with 10% phosphoric acid under cooling. The separated oily material was collected and dissolved in sodium bicarbonate-saturated-aqueous solution. The solution was adjusted to pH 2 with 10% phosphoric acid, and the precipitated crystals were collected by filtration to give 3 - [2 - {4 - (3-benzamido - 3 - carboxypropoxy)phenyl} - 2 - (3 - phenylthioureido)acetamido]lacta-cillanic acid (9.6 g.). Mp 133 to 138°C (dec.).

The following compounds were prepared in substantially the similar manner as described in Example 502.



Example	Compound (XXIX) R_{28}	Acylating agent	Compound (XXX)		
			R_{28}	R_{29}	mp(°C)(dec.)
503			the same as R_{28} of Compound (XXIX)		170 - 172
504			"		190 - 195
505			"		169 - 173
506	$C_2H_5O-\underset{\underset{S}{\Vert}}{C}-NH-$	$C_2H_5O-\underset{\underset{S}{\Vert}}{C}-SCH_3$	"	$C_2H_5O-\underset{\underset{S}{\Vert}}{C}-NH-$	112 - 119

Example 507.

3 - [2 - {4 - (3 - Amino - 3 - carboxypropoxy)phenyl} - 2 - hydroxyiminoacetamido]lactacillanic acid (2.0 g.) suspended in water (20 ml.) was dissolved by adding 1N-sodium hydroxide aqueous solution (4.5 ml.) thereto, and then sodium hydroxymethanesulfonate (1 hydrate) (0.66 g.) was added to said solution.

The mixture was stirred at ambient temperature for 2.5 hrs. The reaction mixture was filtered, and the filtrate was concentrated to about two third of its original volume under reduced pressure. Acetone (40 ml.) was added to the residue, and the precipitated powder was collected by filtration to give disodium salt of 3 - [2 - [4 - {3-carboxy - 3 - (N - sulfomethylamino)propoxy}phenyl] - 2 - hydroxyiminoacetamido]-lactacillanic acid (1.85 g.).

I.R. absorption spectrum,

ν cm^{-1} (Nujol): 1730, 1600, 1240.

Example 508.

3 - [4 - (3 - Amino - 3 - carboxypropoxy)phenylglyoxyloylamino]lactacillanic acid (0.50 g.) suspended in water (10 ml.) was dissolved by adding 1N-sodium hydroxide aqueous solution (1.1 ml.) thereto. Sodium hydroxymethanesulfonate (1 hydrate) (0.152 g.) was added to said solution, and the mixture was stirred at ambient temperature for 4 hrs. The water was distilled off from the reaction mixture under reduced pressure, and the residue was pulverized with acetone. The powder (0.49 g.) was dissolved in a small amount of water, and acetone was added gradually to said solution. The precipitated crystals were collected by filtration to give disodium salt of 3 - [4 - {3 - carboxy - 3 - [N - sulfomethylamino)propoxy}phenylglyoxyloylamino]-lactacillanic acid (63 mg.).

I.R. absorption spectrum,

ν cm^{-1} (Nujol): 1720, 1650, 1260.

Example 509.

A mixture of 3 - [2 - {4 - (3 - amino - 3 - carboxypropoxy)phenyl} - 2-hydroxyiminoacetamido]lactacillanic acid (500 mg.) in water (6 ml.) was dissolved by adding 1N-sodium bicarbonate aqueous solution (1.2 ml.) under cooling. To the solution, there was added a solution of acetaldehyde (220 mg.) and sodium hydrogensulfite (520 mg.) dissolved in water (5 ml.), and the mixture was stirred at room temperature for 3 hrs. and further at 45°C for an hour. The reaction mixture was concentrated to about one third of its original volume under reduced pressure. Ethanol (10 ml.) was added to the residue, and the precipitated crystals were collected by filtration to give 3 - [2 - [4 - [3 - carboxy - 3 - {N - (1 - sulfoethyl)amino}propoxy]phenyl] - 2-hydroxyiminoacetamido]lactacillanic acid disodium salt (0.3 g.). Mp 224.5 to 229°C (dec.).

Example 510.

3 - [2 - {2 - (2 - Carboxyphenylthio)acetamido} - 2 - phenylacetamido]lactacillanic acid (169 mg.) was dissolved in acetone (6 ml.), and 85% 3-chloroperbenzoic acid (61 mg.) was added to the solution under ice-cooling, and then the mixture was stirred at the same temperature for an hour. After the reaction mixture was concentrated under reduced pressure, ethyl acetate (about 3 ml.) was added to the residue and then the solution was stirred for 2 hrs. The precipitated crystals were collected by filtration, washed with ethyl acetate and dried to give 3 - [2 - {2 - (2 - carboxyphenylsulfinyl)-acetamido} - 2 - phenylacetamido]lactacillanic acid (120 mg.). Mp 175 to 181°C (dec.).

Example 511.

3 - [2 - [4 - {3 - Carboxy - 3 - (2,2,2 - trifluoroacetamido)propoxy}phenyl] - 2-hydroxyiminoacetamido]lactacillanic acid (0.59 g.) was dissolved in a solution of acetone (10 ml.) and water (10 ml.), and sodium bicarbonate (0.34 g.) and sodium iodide (0.15 g.) were added to the solution and then the mixture was allowed to stand for a while. Chloromethyl pivalate (0.60 g.) was added to said solution, and the mixture was heated under reflux for 4 hrs. The acetone was distilled off from the reaction mixture under reduced pressure, and the residue was added to a mixture of ethyl acetate (20 ml.) and water (20 ml.). The separated ethyl acetate layer was washed with a sodium bicarbonate aqueous solution, water and then a sodium chloride-saturated-aqueous solution respectively, and dried over anhydrous magnesium sulfate. The solvent was distilled off from the ethyl acetate solution under reduced pressure, and the residue was pulverized with benzene. The powder (0.19 g.) thus obtained was chromatographed on silica : gel (10 g.). Elution was conducted with a mixture of chloroform and methanol (99:1), the fractions containing the object compound were collected, and then

the solvent was distilled off from the fractions. The residue was recrystallized from a mixture of ether and diisopropyl ether to give 1 - (α - pivaloyloxymethoxycarbonyl-4 - hydroxybenzyl) - 3 - [2 - [4 - {3 - pivaloyloxymethoxycarbonyl - 3 - (2,2,2 - trifluoroacetamido)propoxy}phenyl] - 2 - hydroxyiminoacetamido] - 2 - azetidinone (0.12 g.). Mp 135 to 140°C (dec.).

Example 512.

Triethylamine (1.0 g.) and pyridine (6.4 g.) was added to a solution of 3 - [2-[4 - {3 - carboxy - 3 - (3 - phenylthioureido)propoxy}phenyl] - 2 - (2 - phenylthioureido)acetamido]lactacillanic acid (3.04 g.) dissolved in dried acetone (30 ml.). The mixture, after stirred for a while, was cooled to −20 to −15°C, and a solution of 2,2,2-trichloroethyl chloroformate (2.1 g.) dissolved in dried acetone (20 ml.) was added dropwise thereto in 15 minutes, and then the mixture was stirred at the same temperature for 2 hrs. The acetone was distilled off from the reaction mixture under reduced pressure, and the residue was added to a mixture of water (200 ml.) and ethyl acetate (200 ml.). The ethyl acetate layer was separated, washed with a sodium bicarbonate aqueous solution and a sodium chloride-saturated-aqueous solution, and then dried over anhydrous magnesium sulfate. The solvent was distilled off from the ethyl acetate layer, and the residue was pulverized with ether. The powder (1.2 g.) thus obtained was chromatographed on silica : gel (50 g.). Elution was conducted with a mixture of chloroform and methanol (99.1). The fractions containing the object compound were collected, and the solvent was distilled off to give 1 - [α - (2,2,2 - trichloroethoxycarbonyl) - 4 - hydroxybenzyl] - 3 - [2 - [4 - {3 - (3 - phenylthioureido) - 3-(2,2,2 - trichloroethoxycarbonyl)propoxy}phenyl] - 2 - (3 - phenylthioureido)acetamido] - 2 - azetidinone (0.16 g.).

I.R. absorption spectrum,

ν cm^{-1} (Nujol): 1750, 1680, 1220.

Example 513.

An ether solution of diazomethane was added dropwise to a solution of 3 - [2 - {4-(3 - acetamido - 3 - carboxypropoxy)phenyl} - 2 - hydroxyiminoacetamido]lactacillanic acid (5.5 g.) dissolved in methanol (150 ml.) until the color of the diazomethane came to not disappear in the latter solution. The reaction mixture was allowed to stand overnight in a refrigerator, and the solvent was distilled off. The residue was chromatographed on silica : gel. Elution was conducted with a mixture of chloroform and methanol (98:2), and the fractions containing the object compound were collected. The solvent was distilled off to give 1 - (α - methoxycarbonyl - 4 - methoxybenzyl) - 3-[2 - {4 - (3 - acetamido - 3 - methoxycarbonylpropoxy)phenyl} - 2 - methoxyiminoacetamido] - 2 - azetidinone (3.50 g.).

N.M.R. absorption spectrum,

δ_{ppm} (CDCl$_3$): 1.95 (3H, s), 2.25 (2H, m), 3.15 (1H, d,d, J=3H$_z$, 6H$_z$), 3.70 (3H, s), 3.74 (3H, s), 3.78 (3H, s), 3.89 (3H, s), 3.96 (2H, t, J=6H$_z$), 4.70 (1H, q, J=8H$_z$), 4.92 (1H, m), 5.52 (1H, s), 6.75 (2H, d, J=9H$_z$), 6.86 (2H, d, J=9H$_z$), 7.20 (2H, d, J=9H$_z$), 7.45 (2H, d, J=9H$_z$)

Example 514.

3 - [2 - [4 - {3 - Carboxy - 3 - (2,2,2 - trifluoroacetamido)propoxy}phenyl] - 2-hydroxyiminoacetamido]lactacillanic acid (2.0 g) was dissolved in a mixture of ether (20 ml.) and methanol (15 ml.), and the solution was ice-cooled. An ether solution of diazomethane was added dropwise to said solution until the color of the diazomethane came to not disappear in the latter solution. The reaction mixture was stirred at the same temperature for 4 hrs. and further at ambient temperature for 2 hrs. The solvent was distilled off from the reaction mixture, and the residue (2.10 g.) was chromatographed on silica : gel (50 g.), and then the elution was conducted with chloroform. The fractions containing the object compound were collected, and the chloroform was distilled off to give 1 - (α - methoxycarbonyl - 4 - methoxybenzyl) - 3 - [2 - [4-{3 - methoxycarbonyl - 3 - (2,2,2 - trifluoroacetamido)propoxy}phenyl] - 2 - methoxyiminoacetamido] - 2 - azetidinone (1.29 g.).

I.R. absorption spectrum,

ν cm^{-1} (liquid film): 1730, 1700, 1650.

Example 515.

3 - [2 - {4 - (3 - Carboxy - 3 - phthalimidopropoxy)phenyl} - 2 - hydroxyiminoacetamido] - 2 - azetidinone (3.50 g.) was dissolved in methanol (30 ml.), and the

solution was ice-cooled. An ether solution of diazomethane was added dropwise to said solution, until the color of the diazomethane came to not disappear in the latter solution. The mixture was stirred for 5 hrs., and then allowed to stand one day and night in a refrigerator. The solvent was distilled off from the reaction mixture, and the residue was chromatographed on silica : gel (80 g.). Elution was conducted with chloroform, and then with a mixture of chloroform and methanol (98:2). The fractions, which were eluted with a mixture of chloroform and methanol were collected and the solvent was distilled off to give 1 - (α - methoxycarbonyl - 4 - methoxybenzyl) - 3 - [2 - {4- (3 - phthalimido - 3 - methoxycarbonylpropoxy)phenyl} - 2 - methoxyiminoacetamido] - 2 - azetidinone (1.20 g.).

N.M.R. absorption spectrum,

δ_{ppm} ($CDCl_3$): 2.70 (2H, s), 3.15 (1H, d, d, J=3Hz, 6Hz), 3.70 (1H, m), 3.75 (6H, s), 3.78 (3H, s), 3.88 (3H, s), 3.94 (2H, m), 5.05 (1H, m), 5.16 (1H, t, J=6Hz), 5.56 (1H, s), 6.62 (2H, d, J=9Hz), 6.84 (2H, d, J=9Hz), 7.20 (2H, d, J=9Hz), 7.38 (2H, d, J=9Hz), 7.74 (4H, m).

Example 516.

An ether solution of diazomethane was added dropwise to a solution of 3 - [2 - {4- (3 - acetamido - 3 - (carboxypropoxy)phenyl} - 2 - acetamidoacetamido] lactacillanic acid (0.70 g.) dissolved in methanol (20 ml.) until the color of the diazomethane came to not disappear in the latter solution. Then, the mixture was allowed to stand over night in a refrigerator. The solvent was distilled off from the reaction mixture and the residue was chromatographed on silica gel (25 g.). Elution was conducted with chloroform, and then with three kind of a mixture of chloroform and methanol (99:1), (98:2) and (97:3). The fractions containing the object compound were collected and the solvent was distilled off to give 1 - (α - methoxycarbonyl - 4 - methoxybenzyl) - 3 - [2- {4 - (3 - acetamido - 3 - methoxycarbonylpropoxy)phenyl} - 2 - acetamidoacetamido] - 2 - azetidinone (0.30 g.).

I.R. absorption spectrum,

ν cm^{-1} ($CHCl_3$): 1745, 1667, 1195.

Example 517.

3 - [4 - (3 - Amino - 3 - carboxypropoxy)phenylglyoxyloylamino] lactacillanic acid (2.50 g.) was dissolved in dimethylsulfoxide (17.5 ml.), and acetic acid (12.5 ml.) and water (12.5 ml.) was added to said solution under ice-cooling, and then the mixture was stirred for a while. To the solution, there was added an aqueous solution of sodium nitrite (0.50 g.) in water (2 ml.), and the mixture was stirred at ambient temperature for 2 hrs. The reaction mixture was added to ice-water (50 ml.) and the solution was extracted with ethyl acetate (50 ml.) three times. The ethyl acetate layer was separated, washed twice with water (20 ml.) and once with a sodium chloride-saturated-aqueous solution, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the residue was crystallized from a mixture of ethyl acetate and ether to give 3 - [4 - (3 - carboxy - 3 - hydroxypropoxy)phenylglyoxyloylamino] lactacillanic acid (0.49 g.). Furthermore, the same object product (0.21 g.) was recovered from the mother liquor. Total yield was 0.70 g. Mp 196 to 201°C (dec.).

Example 518.

3 - [2 - {4 - (3 - Carboxy - 3 - phthalimidopropoxy)phenyl}glycinamido] lactacillanic acid as a starting material was treated in the similar manner as described in Example 517 to give 3 - [2 - {4 - (3 - carboxy - 3 - phthalimidopropoxy)phenyl}- 2 - hydroxyacetamido] lactacillanic acid. Mp 160 to 163°C (dec.).

Example 519.

3 - [2 - Glycinamido - 2 - (2 - thienyl)acetamido] lactacillanic acid (200 mg.) was dissolved in an aqueous solution (5 ml.) of sodium bicarbonate (168 mg.). To the solution. there was added methanol (5 ml.) and then methyl 4-fluoro-3-nitrobenzoate (80 mg.), and the mixture was stirred at 50°C, for 3 hrs. The methanol was distilled off from the reaction mixture under reduced pressure, and the aqueous residue was washed with ethyl acetate. The aqueous solution was adjusted to pH 2 to 3 with 10% hydrochloric acid under cooling and extracted with ethyl acetate twice. The extracts were combined together, washed with water, dried over anhydrous magnesium sulfate and then evaporated to dryness under reduced pressure. The residue (90 mk.) was crystallized from ether to give crude 3 - [2 - {N - (4 - methoxycarbonyl - 2 - nitrophenyl)glycinamido} - 2 - (2 - thienyl)acetamido] lactacillanic acid (70 mg.). Fur-

thermore, this product was chromatographed on silica : gel (2 g.), and the fractions eluted with ethyl acetate were collected, and the solvent was distilled off from the eluate to give the purified same product (11 mg.). Mp 160 to 164°C (dec.).

Example 520.

3-(2-Phenylglycinamido)lactacillanic acid (369 mg.) was dissolved in a solution of sodium carbonate (10 hydrate) (572 mg.) in water (8 ml.). To the solution, was added a solution of 5-chloro-3-phenyl-1,2,4-oxadiazole (180 mg.) dissolved in acetone (7 ml.), and the mixture was allowed to react at ambient temperature for 5 hrs. The reaction mixture was adjusted to pH 7.0 with sodium bicarbonate and washed with ethyl acetate. The aqueous solution thus obtained was adjusted to about pH 3 with diluted hydrochloric acid and then extracted with ethyl acetate. The ethyl acetate layer was separated, washed with water and dried over anhydrous magnesium sulfate, and the solvent was distilled off. The oily residue (270 mg.) was chromatographed on silica : gel (7 g.). The fractions, eluted with a mixture of ethyl acetate and methanol (97:3), were collected, and the solvent was distilled off to give 3 - [2 - phenyl - N-(3 - phenyl - 1,2,4 - oxadiazol - 5 - yl)glycinamido] lactacillanic acid (95 mg.) as powder.

I.R. absorption spectrum,

ν cm^{-1} (Nujol): 1738, 1680, 1618

Example 521.

3-(2-Phenylacetamido)lactacillanic acid (0.19 g.) was suspended in methanol (5 ml.), and to the suspension was added an ether solution containing diazomethane under ice-cooling, continuing to be added until a color of the diazomethane in the reaction mixture was not disappeared. The reaction mixture was stirred for 2 hrs. at the same temperature, and then the reaction mixture was concentrated under reduced pressure. The residue obtained was dissolved in chloroform, and the solution was washed with a sodium bicarbonate aqueous solution, water and a sodium chloride-saturated-aqueous solution respectively, and then dried over anhydrous magnesium sulfate. The chloroform was distilled off from the solution under reduced pressure to give a residue which was powdered with ether. The powder was collected by filtration to give 1 - (α-methoxycarbonyl - 4 - methoxybenzyl) - 3 - (2 - phenylacetamido) - 2 - azetidinone (0.12 g.), which was recrystallized from ether to give the purified object compound (0.06 g.). Mp 145 to 146°C (dec.).

Example 522.

3 - [2 - {4 - (3 - Amino - 3 - carboxypropoxy)phenyl} - 2 - hydroxyiminoacetamido] lactacillanic acid (3.0 g.) was dissolved in a methanol solution (60 ml) containing sodium hydroxide (480 mg.). To the solution was added a methanol solution (20 ml.) containing methyl acetoacetate (835 mg.), and the mixture was heated for 6 hrs. at 74°C under stirring. The methanol was distilled off from the reaction mixture, and to the residue obtained was suspendedcd in ethanol (300 ml.). The suspension was stirred for an hour at ambient temperature. The insoluble material was collected by filtration and washed with ether to give 3 - [2 - [4 - {3 - carboxy - 3 - (2 - methoxycarbonyl - 1 - methylvinylamino)propoxy}phenyl] - 2 - hydroxyiminoacetamido]-lactacillanic acid disodium salt (1.2 g.). Furthermore, the mother liquor was concentrated to give a residue, and to the residue was added ether, and then the powder was collected by filtration to recover an object compound (2.4 g.). Total yield was 3.6 g.

N.M.R. absorption spectrum,

δ_{ppm} (D_2O): 1.8 (3H, s), 2.2 (2H, m), 3.1 (1H, m), 3.8 (2H, m), 3.56 (3H, s), 4.1 (2H, broad s), 5.0 (1H, m), 5.3 (1H, s), 6.7—7.5 (8H, m).

Example 523.

3 - [4 - (3 - Benzyloxycarbonyl - 5 - oxo - 1,3 - oxazolidin - 4 - yl)butyramido]-lactacillanic acid (200 mg.) was dissolved in methanol (15 ml.), and to the solution was added 10% palladium : carbon (50 mg.) as a catalyst. The mixture was reacted in hydrogen atmosphere at ordinary atm. A theoretical volume of hydrogen gas was introduced into the mixture in 4 hrs. The reaction mixture was subjected to filtration, and the filtrate was concentrated under reduced pressure. The residue obtained was pulverized with acetone and the powder was collected by filtration to give 3-(5-amino-5-carboxyvalerylamino)lactacillanic acid (97 mg.).

N.M.R. absorption spectrum,
δ_{ppm} (D_2O+$NaHCO_3$): 1.64—1.90 (4H, m), 2.24 (2H, t, J=4Hz), 2.90, 2.94 (1H, d, d, J=2Hz, 6Hz), 3.67 (1H, t, J=6Hz), 5.19 (1H, s), 6.79 (2H, d, J=8Hz), 7.12 (2H, d, J=8Hz).

Example 524.

3 - [2 - [2 - {4 - Chloro - 2 - (4 - nitrobenzoyl)phenoxy}acetamido] - 2 - phenylacetamido]lactacillanic acid (103 mg.) was dissolved in methanol (15 ml.). To the solution was added 10% palladium : carbon (45 mg.) as a catalyst, and the mixture was stirred in hydrogen atmosphere. A calculated volume of hydrogen was absorbed into the mixture in 2.5 hrs. The methanol was distilled off from the reaction mixture, and the residue (80 mg.) obtained was washed with ether to give 3 - [2 - [2 - {2 - (4-aminobenzoyl) - 4 - chlorophenoxy}acetamido] - 2 - phenylacetamido]lactacillanic acid (70 mg.). Mp 150 to 153°C (dec.).

Example 525.

3 - [2 - {2 - (2 - Phenoxycarbonylphenoxy)acetamido} - 2 - phenylacetamido]-lactacillanic acid (190 mg.) and 80% hydrazine hydrate aqueous solution (60 mg.) were dissolved in methanol (6 ml.), and the solution was stirred for 3 hrs. at ambient temperature. The methanol was distilled off from the reaction mixture to give a residue which was powdered with ether. A small amount of ethanol was added to the powder (180 mg.) and the mixture was stirred for an hour, whereafter an insoluble material was collected by filtration to give 3 - [2 - {2 - (2 - hydrazinocarbonylphenoxy)-acetamido} - 2 - phenylacetamido]lactacillanic acid hydrazine salt (100 mg.). Mp 178 to 182°C (dec.).

Example 526.

3 - [2 - {4 - (3 - Azidopropoxy)phenyl}acetamido]lactacillanic acid (52 mg.) was dissolved in methanol (10 ml.). To the solution was added 10% palladium carbon as a catalyst, and the mixture was stirred in hydrogen atmosphere. A calculated volume of hydrogen was absorbed into the mixture in 1.5 hrs. The catalyst was filtered off from the reaction mixture, and the methanol was distilled off from the filtrate. The residue obtained was treated with acetone to give 3 - [2 - {4 - (3 - aminopropoxy)phenyl}-acetamido]lactacillanic acid (38 mg.).

I.R. absorption spectrum,
ν cm^{-1} (Nujol): 1730, 1660, 1610.

Example 527.

3-(2-Ethoxalylamino-2-phenylacetamido)lactacillanic acid (200 mg.) was dissolved in ethanol (4 ml.), and to the solution was added an ethanol solution (3.5 ml.) containing benzylamine (136 mg.), and then the mixture was stirred for 6.5 hrs. at ambient temperature. The reaction mixture was concentrated to give a residue which was poured into a mixture of water and ethyl acetate. 1N-Hydrochloric acid (1 ml.) was added to the mixture, and then the ethyl acetate layer was separated out and washed with 1% hydrochloric acid and water respectively. The ethyl acetate layer was dried over anhydrous magnesium sulfate whereafter the solvent was distilled off from the solution to give a residue which was washed with diisopropyl ether to give crystals (160 mg.). The crystals were recrystallized from a mixture of acetone and ethyl acetate to give crystals of 3 - [2 - (N - benzyloxamoyl)amino - 2 - phenylacetamido]lactacillanic acid (70 mg.). Mp 149 to 154°C (dec.).

Example 528.

An acetone solution (2 ml.) containing 2-phenylacetylchloride (240 mg.) was added dropwise to a mixture of 3-guanidinocarbonylaminolactacillanic acid (160 mg.), 0.1N-potassium hydroxide aqueous solution (10 ml.), sodium bicarbonate (130 mg.), water (5 ml.) and acetone (10 ml.) at 0 to 5°C, and the mixture was stirred for 3.5 hrs. at the same temperature to give crystals of 3 - [3 - (2 - phenylacetyl)guanidinocarbonylamino]lactacillanic acid (120 mg.). Mp 159 to 161°C (dec.).

Example 529.

3-[2-(4-Formylphenoxy)acetamido]lactacillanic acid (200 mg.) was dissolved in 0.1N-sodium hydroxide aqueous solution under ice-cooling. To the solution was added sodium borohydride (20 mg.), and the mixture was stirred for 50 minutes. Acetone (0.5 ml.) and ethyl acetate (10 ml.) were added to the reaction mixture, and then the mixture was adjusted to pH 1 to 2 with 1N-hydrochloric acid. The ethyl acetate layer

was separated out, and washed with water and a sodium chloride aqueous solution, respectively, and then dried over anhydrous magnesium sulfate. The solvent was distilled off from the solution, and the residue obtained was crystallized from ethyl acetate to give 3-[2-(4-hydroxymethylphenoxy)acetamido]lactacillanic acid (110 mg.). Mp 182 to 185°C (dec.).

Example 530.

3 - [2 - {2 - (2 - Formylphenoxy)acetamido} - 2 - phenylacetamido]lactacillanic acid (200 mg.) was treated in substantially the similar manner as described in Example 529 to give 3 - [2 - {2 - (2 - hydroxymethylphenoxy)acetamido} - 2 - phenylacetamido]lactacillanic acid (130 mg.). Mp 95 to 101°C (dec.).

Example 531.

3-(2-Phenyl-2-phenylglyoxyloylaminoacetamido)lactacillanic acid (170 mg.) was dissolved in 0.1N-sodium hydroxide aqueous solution (3.5 ml.), and to the solution was added dropwise an aqueous solution (1 ml.) containing sodium borohydride (13 mg.), and then the mixture was stirred for 40 minutes. To the reaction mixture was added ethyl acetate (30 ml.), and the mixture was adjusted to pH 1 with 10% hydrochloric acid. The ethyl acetate layer was separted, and the remaining aqueous solution was extracted with ethyl acetate (20 ml.). These extracts were combined washed with a sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. The solvent was distilled off from the solution, and the residue obtained was powdered with ether to give 3-[2-(2-phenylglycolamido)-2-phenylacetamido]lactacillanic acid (140 mg.). Mp 90 to 93°C (dec.).

Example 532.

Sodium borohydride (40 mg.) was added to a mixture of 3-[2-(4-formylphenoxy)-acetamido]lactacillanic acid (200 mg.), 0.1N-sodium hydroxide aqueous solution (5 ml.), benzylamine (106 mg.) and ethanol (2 ml.) under ice-cooling, and the reaction mixture was stirred for 30 minutes at the same temperature. The reaction mixture was washed with ether twice, and adjusted to about pH 4 with 10% hydrochloric acid to give an isolating oily material which was separated by decantation. The oily material was powdered with acetone, and the powder was collected by filtration and washed with acetone to give 3-[2-(4-benzylaminomethylphenoxy)acetamido]lactacillanic acid (105 mg.). Mp 172 to 177°C (dec.).

Example 533.

3 - [2 - {4 - (1 - Benzyloxycarbonylamino - 1 - methoxycarbonylmethyl)phenoxy}acetamido]lactacillanic acid (200 mg.) was dissolved in methanol (15 ml.). To the solution was added 10% palladium carbon (35 mg.) as a catalyst, and the mixture was reacted for 2 hrs. in hydrogen atmosphere at ordinary temperature and ordinary atm. After a calculated volume of hydrogen was absorbed into the mixture, the catalyst was filtered off from the reaction mixture, and then the filtrate was concentrated under reduced pressure. The residue obtained was powdered with acetone and treated with acetone to give 3 - [2 - {4 - (1 - amino - 1 - methoxycarbonylmethyl)phenoxy}-acetamido]lactacillanic acid (90 mg.). Mp 190 to 194°C (dec.).

Example 534.

3 - [2 - {4 - (2 - Benzyloxycarbonylamino - 2 - methoxycarbonylethyl)phenoxy}-acetamido]lactacillanic acid (1.35 g.) was dissolved in 1N-sodium hydroxide aqueous solution (6.7 ml.), and the solution was stirred for an hour at ambient temperature. A small amount of water was added to the reaction mixture, and then the solution was washed with ethyl acetate, whereafter the aqueous solution was adjusted to pH 1 with 1N-hydrochloric acid. The solution was extracted with ethyl acetate and the ethyl acetate layer was separated out, and washed with water and then dried over anhydrous magnesium sulfate. The solvent was distilled off from the solution, and the residue was crystallized from chloroform to give crystals of 3-[2-{4-(2-benzyloxycarbonylamino-2-carboxyethyl)phenoxy}acetamido]lactacillanic acid (1.07 g.). Mp 125 to 130°C (dec.).

Example 535.

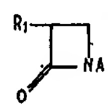
3 - [2 - {4 - (1 - Benzyloxycarbonylamino - 1 - methoxycarbonylmethyl)phenoxy}acetamido]lactacillanic acid (118 mg.) was dissolved in 0.1N-sodium hydroxide aqueous solution (4 ml.), and the solution was stirred for 2 hrs. at ambient temperature. Subsequently, 0.1N-hydrochloric acid (4 ml.) was added to the reaction mixture, and then the solution was extracted with ethyl acetate. The extract was washed with water and dried over anhydrous magnesium sulfate. The solvent was distilled off from the

solution, and the residue was crystallized from a small amount of acetone. The crystals were treated with ethyl acetate to give crystals of 3-[2-{4-(1-benzyloxycarbonylamino-1-carboxymethyl)phenoxy}acetamido]lactacillanic acid (30 mg.). Mp 134 to 138°C (dec.).

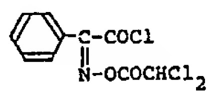
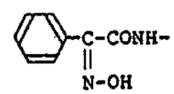
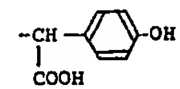
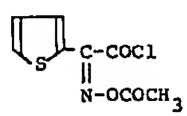
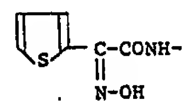
Example 536.

2-(4-Benzyloxyphenyl)-2-(2,2-dichloroacetoxyimino)acetic acid (0.382 g.) was suspended in benzene (7 ml.) and the suspension was cooled to 0 to 5°C. To the suspension was added all at once phosphorus pentachloride (0.250 g.), and the mixture was stirred for an hour at the same temperature. The benzene was distilled off from the mixture under reduced pressure under water-cooling. Benzene (7 ml.) was added to the residue, and the benzene was distilled off from the solution under reduced pressure, and this operation was repeated three times. The residue obtained was dissolved in dried methylene chloride (10 ml.). On the other hand, 3-aminolactacillanic acid (0.236 g.) was suspended in dried methylene chloride (20 ml.), and to the suspension was added N,O-bis(trimethylsilyl)acetamide (0.87 g.), and the mixture was stirred for a while at ambient temperature. This solution was added to the methylene chloride solution obtained above under cooling at 0 to 5°C in 30 minutes, and the reaction mixture was stirred for an hour at the same temperature. The reaction mixture was washed with water, and concentrated under reduced pressure to give a residue. Ethyl acetate and 5% sodium bicarbonate aqueous solution were added to the residue, and the mixture was stirred enough. The aqueous layer was separated out, and adjusted to pH 1 to 2, and then extracted with ethyl acetate. The ethyl acetate layer was separated out and dried over anhydrous magnesium sulfate. The solvent was distilled off from the layer obtained under reduced pressure to give an oily residue which was washed with ether and powdered with chloroform. The powder (108 mg.) obtained was dissolved in acetone (2 ml.), and to the solution was added an aqueous solution (1.2 ml.) containing sodium 2-ethylhexanate (612 mg.). To the mixture was added ether (3 ml.) to give a powder which was collected by filtration. The powder was washed with ether and dissolved in water. The aqueous solution was adjusted to pH 1 to 2 with diluted hydrochloric acid, and then the solution was extracted with ethyl acetate. The extract was washed with water and dried over anhydrous magnesium sulfate. The solvent was distilled off from the solution, and the residue was crystallized from chloroform to give crystals of 3-[2-(4-benzyloxyphenyl)-2-hydroxyimino]lactacillanic acid (95 mg.). Mp 137 to 140°C (dec.).

The following compounds were obtained in substantially the similar manner as described above.



(I)

Example	Acylating agent	Compound (I)		
		R_1	A	mp(°C) (dec.)
537				197 - 199
538			"	N.M.R. δ ppm (CD_3OD): 3.25(1H,m) 3.90(1H,m) 5.10(1H,m) 5.50(1H,s) 6.85(2H,d,J=9Hz) 7.2 (1H,m) 7.25(2H,d,J=9Hz) 7.65(1H,d,J=5Hz) 7.95(1H,d,J=4Hz)
539	NC-C(=N-OCOCH$_3$)-COCl	NC-C(=N-OH)-CONH-	"	240 - 245

Example 540.

3 - (2 - Phenylacetamido) - 1 - (α - methoxycarbonyl - 3 - benzyloxycarbonylaminobenzyl) - 2 - azetizinone (14 mg.) was dissolved in isopropyl alcohol (4 ml.), and 10% palladium : carbon (10 mg.) was added as a catalyst to the solution. The reaction mixture was subjected to reaction in hydrogen stream at 50°C under ordinary atmosphere. A calculated volume of hydrogen gas was absorbed into the reaction mixture in an hour. The catalyst was removed by filtration, and the filtrate was concentrated to give oily 3-(2-phenylacetamido)-1-(α-methoxycarbonyl-3-aminobenzyl)-2-azetidinone (7 mg.).

I.R. absorption spectrum,

ν cm^{-1} ($CHCl_3$): 3425, 1755, 1745, 1675, 1620

Example 541.

3 - [2 - [2 - [4 - Chloro - 2 - {4 - (2 - chloroacetamido)benzoyl}phenoxy] acetamido] - 2 - phenylacetamido] lactacillanic acid (150 mg.) and 30% trimethylamine aqueous solution (160 mg.) was dissolved in methanol (4 ml.), and the solution was stirred at 50°C for 1.5 hrs. 30% Trimethylamine aqueous solution (160 mg.) was added to said solution four times, respectively every an hour. The solvent was distilled off from the reaction mixture, and the residue was washed with acetone, whereafter water (5 ml.) was added to the residue (150 mg.), and the mixture was stirred for 30 minutes. The insoluble material was collected by filtration, and acetone (10 ml.) was added to the material. The mixture was stirred for 30 minutes and the insoluble material was collected by filtration to give crystals of N - [N - [4 - [3 - chloro - 2 - [N - [1-[N - {1 - (α - carboxy - 4 - hydroxybenzyl) - 2 - oxo - 3 - azetidinyl}carbamoyl] - 1-phenylmethyl] carbamoylmethoxy] benzoyl] phenyl] carbamoylmethyl] - N,N,N - trimethylammonium chloride (120 mg.). Mp 214 to 220°C (dec.).

Example 542.

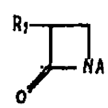
3 - [2 - {4 - (3 - Amino - 3 - carboxypropoxy)phenyl} - 2 - hydroxyiminoacetamido] lactacillanic acid (1.0 g.) was dissolved in a mixture of 1N-sodium hydroxide aqueous solution (4 ml.) and water (20 ml.). A methanol solution (4 ml.) containing methyl acrylate (0.34 g.) was added to said solution little by little, and the mixture was stirred for 5.5 hrs. under ice-cooling. The reaction mixture was adjusted to pH 3 with 10% hydrochloric acid, and then precipitated crystals were collected by filtration. The crystals were dissolved in a small amount of a sodium bicarbonate aqueous solution, whereafter the solution was adjusted to pH 3 with 10% hydrochloric acid. The precipitated crystals in the aqueous solution were collected by filtration to give crystals of 3 - [2 - [4 - {3 - carboxy - 3 - (2 - methoxycarbonylethylamino)propoxy}phenyl] - 2-hydroxyiminoacetamido] lactacillanic acid (0.57 g.). Mp 175 to 179°C (dec.).

Example 543.

3 - [2 - {2 - Oxo - 3 - (2 - phenylacetamido) - 1 - azetidinyl} - 3 - methylbutyramido] - 2 - azetidinone and benzyl 2 - bromo - 2 - (p - benzyloxyphenyl) acetate were treated in substantially the similar manner as described in Example 224 to give 3 - [2 - {2 - Oxo - 3 - (2 - phenylacetamido) - 1 - azetidinyl} - 3 - methylbutyramido] lactacillanic acid. Mp 160 to 164°C (dec.).

WHAT WE CLAIM IS:—

1. A compound of the formula:



(I)

or its salt

wherein

R_1 is amino or acylamino,

A is hydrogen,

a saturated or unsaturated normal aliphatic hydrocarbon residue, which is substituted by at least one substituent of carboxy or its derivatives, cyano, hydroxy and amino,

an unsaturated branched aliphatic hydrocarbon residue which is substituted by at least one substituent of carboxy, or its derivatives, cyano, hydroxy and amino, or

an aliphatic hydrocarbon residue which is substituted by carboxy or its derivatives at the first position thereof and by phnyl at the first position thereof whose ring may be

substituted by one or more substituents selected from hydroxy, amino, nitro, alkyl, alkoxy, aralkoxy, alkylthio, halogen and sulfo;

provided that when R_1 is 2-[4-(3-amino-3-carboxypropoxy)phenyl]-2-hydroxyiminoacetamido,

A is hydrogen,

a saturated or unsaturated normal aliphatic hydrocarbon residue, which is substituted by at least one substituent of carboxy or its derivatives, cyano, hydroxy and amino,

an unsaturated branched aliphatic hydrocarbon residue which is substituted by at least one substituent of carboxy or its derivatives, cyano, hydroxy and amino, or

an aliphatic-hydrocarbon residue which is substituted by carboxy or its derivatives at the first position thereof and by phenyl at the first position thereof whose ring may be substituted by one or more substituents selected from hydroxy other than 4-hydroxy, amino, nitro, alkyl, alkoxy, aralkoxy, alkylthio, halogen and sulfo,

when

R_1 is 2-(2-nitrophenoxy)acetamido or 2-(2-nitrophenoxy)-2-methylpropionamido,

A is a saturated or unsaturated normal aliphatic-hydrocarbon residue which is substituted by at least one substituent of carboxy or its derivatives, cyano, hydroxy and amino,

an unsaturated branched aliphatic hydrocarbon residue, which is substituted by at least one substituent of carboxy or its derivatives, cyano, hydroxy and amino, or

an aliphatic hydrocarbon residue which is substituted by carboxy or its derivatives at the first carbon thereof and by phenyl at the first carbon thereof, whose ring may be substituted by one or more substituents selected from hydroxy, amino, nitro, alkyl, alkoxy, aralkoxy, alkylthio, halogen and sulfo, and

when

R^1 is phenylacetamido,

A is hydrogen,

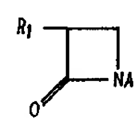
a saturated or unsaturated normal aliphatic hydrocarbon residue, which is substituted by at least one substituent of carboxy or its derivatives, cyano, hydroxy and amino, or

an aliphatic hydrocarbon residue which is substituted by carboxy or its derivatives at the first position thereof and by phenyl at the first position thereof, whose ring may be substituted by one or more substituents selected from hydroxy, amino, nitro, alkyl, alkoxy, aralkoxy, alkylthio, halogen and sulfo,

when

A is hydrogen, R_1 is not formamido, benzyloxycarbonylamino or phthalimido.

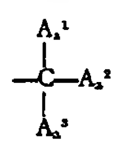
2. A compound of the formula:



wherein

R_1 is amino or acylamino, and

A is hydrogen or a group of the formula:



in which

A_a^1 is hydrogen and

A_a^2 is hydrogen or phenyl which may be substituted by at least one substituent selected from hydroxy, amino, nitro, alkyl, alkoxy, aralkoxy, alkylthio and halogen, or

A_a^1 and A_a^2 together form alkylidene, and

A_a^3 is carboxy or its derivatives, or cyano.

provided that,

when

R_1 is 2-[4-(3-amino-3-carboxypropoxy)phenyl]-2-hydroxyiminoacetamido,

A is not α-carboxy-4-hydroxybenzyl or its derivatives at the carboxy group;

when

R_1 is 2-(2-nitrophenoxy)acetamido, 2-(2-nitrophenoxy)-2-methylpropionamido, formamido, benzyloxycarbonylamino or phthalimido,

A is a group of the formula:

$$\begin{array}{c} A_a^1 \\ | \\ -\mathrm{C}-A_a^2 \\ | \\ A_a^3 \end{array}$$

in which

A_a^1, A_a^2 and A_a^3 are as defined above; and

when

R_1 is phenylacetamido,

A is hydrogen, or a group of the formula:

$$\begin{array}{c} A_a^1 \\ | \\ -\mathrm{C}-A_a^2 \\ | \\ A_a^3 \end{array}$$

in which

A_a^1 is hydrogen,

A_a^2 is hydrogen or phenyl which may be substituted by at least one substituent selected from hydroxy, amino, nitro, alkyl, alkoxy, aralkoxy, alkylthio, and halogen, and

A_a^3 is as defined above.

3. A compound according to claim 2, wherein R_1 is amino or acylamino excepting 2-(2-nitrophenoxy)acetamido, 2-(2-nitrophenoxy)-2-methylpropionamido, formamido, benzyloxycarbonylamino and phthalimido, and A is hydrogen.

4. A compound according to claim 3, wherein R_1 is aralkanoylamino or aryloxyalkanoylamino.

5. A compound according to claim 4, wherein R_1 is phenylacetamido or phenoxyacetamido.

6. A compound according to claim 2, wherein R_1 is acylamino, and A is a group of the formula: $-CH_2-A_a^3$, in which A_a^3 is as defined in claim 2.

7. A compound according to claim 6, wherein R_1 is aralkanoylamino.

8. A compound according to claim 7, wherein R_1 is phenylacetamido, and A_a^3 is carboxy or its derivatives.

9. A compound according to claim 7, wherein R_1 is phenylacetamido, and A_a^3 is cyano.

10. A compound according to claim 2, wherein

R_1 is amino or acylamino excepting phenylacetamido, and

A is a group of the formula:

$$\begin{array}{c} A_a^1 \\ | \\ -\mathrm{C}-A_a^2 \\ | \\ A_a^3 \end{array}$$

in which

A_a^1 and A_a^2 together form alkylidene, and

A_a^3 is carboxy or its derivatives.

11. A compound according to claim 10, wherein R_1 is amino or aryloxyalkanoylamino.

12. A compound according to claim 11, wherein R_1 is amino or phenoxyacetamido, and A is 1-carboxy-2-methyl-1-propenyl or its derivative at the carboxy group.

13. A compound according to claim 2, wherein

R_1 is amino or acylamino, and

A is a group of the formula:

$$\begin{array}{l} -\mathrm{CH}-A_a^2 \\ \;\;| \\ \;\;A_a^3 \end{array}$$

in which

A_a^2 is phenyl which may be substituted by at least one substituent selected from hydroxy, amino, nitro, alkyl, alkoxy, aralkoxy, alkylthio and halogen, and

A_a^3 is carboxy or its derivatives,

provided that,

when

R_1 is 2-[4-(3-amino-3-carboxypropoxy)phenyl]-2-hydroxyiminoacetamido,

A is not α-carboxy-4-hydroxybenzyl or its derivative at the carboxy group.

14. A compound according to claim 13, wherein A_a^2 is phenyl.

15. A compound according to claim 13, wherein A_a^2 is hydroxyphenyl, provided that when R_1 is 2-[4-(3-amino-3-carboxypropoxy)phenyl]-2-hydroxyiminoacetamido, A_a^2 is not 4-hydroxyphenyl.

16. A compound according to claim 15, wherein A_a^2 is 4-hydroxyphenyl, provided that R_1 is not 2-[4-(3-amino-3-carboxypropoxy)phenyl]-2-hydroxyiminoacetamido.

17. A compound according to claim 13, wherein A_a^2 is aminophenyl.

18. A compound according to claim 17, wherein A_a^2 is 3-aminophenyl.

19. A compound according to claim 13, wherein A_a^2 is nitrophenyl.

20. A compound according to claim 19, wherein A_a^2 is 3-nitrophenyl.

21. A compound according to claim 13, wherein A_a^2 is alkylphenyl.

22. A compound according to claim 21, wherein A_a^2 is 4-methylphenyl.

23. A compound according to claim 13, wherein A_a^2 is alkoxyphenyl.

24. A compound according to claim 23, wherein A_a^2 is 4-methoxyphenyl.

25. A compound according to claim 13, wherein A_a^2 is trialkoxyphenyl.

26. A compound according to claim 25, wherein A_a^2 is 3,4,5-trimethoxyphenyl.

27. A compound according to claim 13, wherein A_a^2 is aralkoxyphenyl.

28. A compound according to claim 27, wherein A_a^2 is 4-benzyloxyphenyl.

29. A compound according to claim 13, wherein A_a^2 is alkylthiophenyl.

30. A compound according to claim 29, wherein A_a^2 is 4-methylthiophenyl.

31. A compound according to claim 13, wherein A_a^2 is halo- and hydroxy-phenyl.

32. A compound according to claim 31, wherein A_a^2 is 3-bromo-4-hydroxyphenyl.

33. A compound according to claim 13, wherein A_a^2 is dihalo- and hydroxy-phenyl.

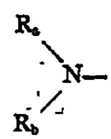
34. A compound according to claim 33, wherein A_a^2 is 3,5-dichloro-4-hydroxyphenyl.

35. A compound according to claim 33, wherein A_a^2 is 3,5-dibromo-4-hydroxyphenyl.

36. A compound according to claim 13, wherein

A is as defined in claim 13, and

R_1 is a group of the formula:



wherein

R_a and R_b are each hydrogen;

R_a is hydrogen and

R_b is arenesulfonyl;

R_a and R_b together form a bivalent acyl group derived from a dicarboxylic acid; or

R_a is hydrogen and

R_b is

4-aminobenzoyl,

3,5-diaminobenzoyl,

2-[4-(2-chloroacetyl)phenyl]acetyl,

3-phenylacryloyl,

4-(2-phenoxyacetamido)benzoyl,

3-(2-chlorophenyl)-5-methyl-4-isoxazolecarbonyl,

2,2-dimethylpropionyl,

3-(3-oxo-1,2-oxazolidin-4-yl)carbamoyl,

3-methylthioacryloyl,

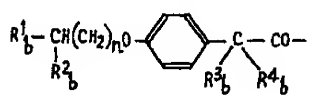
2 - [2 - [4 - chloro - 2 - {4 - (2 - bromoacetamido)benzoyl}phenoxy]acetamido] - 2 - phenylacetyl,

2 - [2 - benzyloxyimino - 2 - (4 - methoxyphenyl)acetamido] - 2 - phenylacetyl,

2 - [4 - (4 - chloroanilinomethyl)phenoxy] - 2 - methylpropionyl,

2 - [2 - [4 - chloro - 2 - [4 - {2 - (2 - pyridylthio)acetamido}benzoyl]phenoxy]-acetamido] - 2 - phenylacetyl, or

an acyl group selected from the following groups:—



n is an integer 0—4,
R_b^1 is hydrogen; or carboxy or its derivative;
R_b^2 is hydroxy; halogen; azido; amino; an aliphatic radical-amino selected from alkylamino, alkenylamino and cycloalkylamino; arylamino; acylamino selected from alkanoylamino, alkoxy(thiocarbonyl)amino, aryloxyalkanoylamino, aralkanoylamino, heterocyclicalkanoylamino and aroylamino; N′-arylureido; N′-arylthioureido; or arylthio;
R_b^3 is hydrogen; hydroxy; amino; arylamino; acylamino selected from alkanoylamino, alkoxy(thiocarbonyl)amino, and aroylamino, N′-arylureido; or N′-arylthioureido;
R_b^4 is hydrogen, or
R_b^3 and R_b^4 together form oxo; hydroxyimino; or alkoxyimino,
in which the aliphatic hydrocarbon moiety may be substituted by at least one suitable substituent of carboxy or its derivative, halogen and sulfo, and the aryl and heterocyclic ring may be substituted by at least one suitable substituent or nitro, halogen, carboxy or its derivative;

(ii) $R_b^6—\underset{\underset{R_b^5}{\|}}{C}—CO—$:

in which
R_b^5 is oxo; hydroxyimino; or substituted hydroxyimino selected from alkoxyimino and aralkoxyimino;
R_b^6 is cyano; alkyl; aryl; heterocyclic radical; alkylamino; aralkylamino; or alkoxy;
in which the alkyl moiety may be substituted by at least one suitable substituent selected from hydroxy and carboxy or its derivative, and the aryl and heterocyclic ring may be substituted by at least one substituent of hydroxy, alkoxy which may have carboxy or its derivative, alkenyloxy and aralkoxy.

(iii) $R_b^7—CO—$:

in which

R_b^7 is aryl; aryloxy; aralkyloxy; arylamino; a heterocyclic radical; guanidino; or 3-aralkanoylguanidino;
in which an aryl and a heterocyclic radical may be substituted by at least one suitable substituent of nitro, halogen, alkyl and alkoxy, and

(iv) $R_b^9—(CH_2)_{n_2}—\underset{\underset{R_b^8}{|}}{CH}—(CH_2)_{n_3}—CO—$:

in which
n_2 and n_3 are each 0 or an integer 1—4,
R_b^8 is hydrogen; alkyl; aryl; aryloxy; a heterocyclic radical; or N-arylcarbamoyl;
in which the aryl and heterocyclic radical may be substituted by at least one suitable substituent.
R_b^9 is hydrogen; amino; azido; halogen; hydroxy; carboxy or its derivative; sulfo; arylsulfo; an aliphatic radical selected from alkyl and alkenyl,
which may be substituted by at least one suitable substituent selected from amino, protected amino, azido, halogen, hydroxy, carboxy or its derivative, sulfo, aroyl, N-alkyl-N-arylamino, aryl, substituted aryl, a heterocyclic radical and a substituted heterocyclic radical;

aryl
which may be substituted by at least one suitable substituent selected from hydroxy, nitro, carboxy, halogen and arenesulfonamido which may have at least one substituent selected from carboxy and hydroxy;

a heterocyclic radical;

an alkyl-heterocyclic radical;
an aryl-heterocyclic radical;
a heterocyclic-heterocyclic radical;
a heterocyclic-alkanoyl-amino-heterocyclic radical;

an aralkanoylamino-heterocyclic radical,
in which an aryl and heterocyclic rings may have at least one suitable substituent selected from oxo and halogen;

aroyl;

aliphatic radical-oxy selected from alkoxy, and cycloalkyloxy,
which may be substituted by at least one suitable substituent;

aryloxy
whose aryl ring may be substituted by at least one substituent selected from nitro, halogen, alkanoyl, alkanoylamino, aryl, aralkylamino, and an aliphatic radical selected from alkyl and alkenyl, in which the aliphatic radical may be substituted by at least one suitable substituent selected from carboxy or its derivative, amino, hydroxy, nitro, hydroxyimino, alkoxyimino [in which the alkane moiety may be substituted by carboxy], (N-halo-N,N,N-trialkylammonio)alkanoylhydrazono, and alkylthioalkanoylamino, in which an alkyl-thio moiety may be substituted by at least one suitable substituent selected from amino and carboxy;

heterocyclic-oxy;
alkylthio;
alkenylthio;
aroylalkanoylamino-alkylthio;

acyl-aliphatic radical-thio selected from aroylalkylthio and N-arylcarbamoylalkylthio
which may have at least one suitable substituent selected from halogen and nitro;
alkylsulfinyl;
N-arylcarbamoylalkylsulfinyl;

arylthio
which may be substituted by carboxy;

heterocyclic-thio;
aminoalkyl-heterocyclic-thio;

alkanoylaminoalkyl-heterocyclic-thio
which may be substituted by hydroxy;

arylamino
which may be substituted by at least one suitable substituent selected from oxo-substituted heterocyclic-amino;

aryl-heterocyclic-amino;

mono- or di-substituted amino selected from alkylamino, N-alkyl-N-(protected carboxy)-amino, N-alkanoyl-N-arylamino, N-alkyl-N-arylamino,
in which an aliphatic hydrocarbon moiety may have at least one suitable substituent selected from azido and carboxy, and N-alkanesulfonyl-N-arylamino;

acylamino selected from:—

alkanoylamino,
which may be substituted by at least one suitable substituent selected from halogen and amino;
cycloalkyloxyalkanoylamino,
which may be substituted by at least one suitable substituent;

alkylthioalkanoylamino;
in which an aliphatic hydrocarbon moiety may be substituted by at least one suitable substituent selected from amino, halogen and carboxy;

alkoxy-aralkanoylamino;

aryloxy-aralkanoylamino,
in which an aliphatic hydrocarbon moiety and an aryl ring may have at least one suitable substituent selected from halogen, aralkoxyimino, arylamino, amino and hydroxy;

arylaminoalkanoylamino,
in which an aryl ring and an aliphatic hydrocarbon moiety may be substituted by at least one suitable substituent selected from halogen, carboxy and amino;

aryloxyalkanoylamino,
which may be substituted by at least one suitable substituent of halogen, nitro, carboxy, formyl and carbazoyl.

alkyl-aryloxyalkanoylamino,
which may be substituted by hydroxy;

aryl-aryloxyalkanoylamino;

aralkyl-aryloxyalkanoylamino,
which may be substituted by at least one suitable substituent selected from hydroxyimino and halogen;

formyl-aryloxyalkanoylamino;
alkanoyl-aryloxyalkanoylamino;

aroyl-aryloxyalkanoylamino
which may be substituted by at least one suitable substituent selected from nitro, amino and halogen;

alkylthioalkanoylaminoaroyl-aryloxyalganoylamino,
which may be substituted by at least one suitable substituent selected from halogen, amino and carboxy;

alkylthioalkylaminoaroyl-aryloxyalkanoylamino,
which may be substituted by at least one suitable substituent selected from amino and halogen;

(N-halo-N,N,N-trialkylammonio)alkanoylaminoaroyl-aryloxyalkanoylamino
which may be substituted by halogen;

heterocyclic-carbonyl-aryloxyalkanoylamino,
which may be substituted by halogen;

aralkylaminoalkyl-aryloxyalkanoylamino,
which may be substituted by at least one suitable substituent of alkoxy, carboxyalkoxy and carboxy;

heterocyclic-aryloxyalkanoylamino,
in which a heterocyclic ring may be substituted by at least one suitable substituent selected from alkyl, aryl and haloaryl, and the alkane moiety may be substituted by at least one suitable substituent selected from halogen and amino;

diaryloxyalkanoylamino,
in which an aliphatic hydrocarbon moiety may be substituted by at least one suitable substituent selected from halogen and amino;

arylthioalkanoyl amino,
which may be substituted by carboxy;

heterocyclic-aliphatic acylamino,
in which the heterocyclic radical may have at least one suitable substituent selected from alkyl, aryl which may have a halogen substituent, and the aliphatic hydrocarbon moiety may have at least one suitable substituent selected from halogen and amino;

heterocyclic-heterocyclic-alkanoyl;

heterocyclic-thioalkanoylamino
which may be substituted by at least one suitable substituent selected from hydroxy, amino, and alkyl which may have at least one substituent;

aralkanoylamino-alkanoylamino,
in which aliphatic hydrocarbon moiety and/or aryl ring may be substituted by at least one suitable substituent selected from amino, halogen and carboxy;

arylsulfinylalkanoylamino,
which may be substituted by carboxy;

arylsulfoalkanoylamino;
(N-aryl-N-arylsulfonylamino)alkanoylamino;
arylglyoxyloylamino;
alkoxalylamino;
aralkylaminooxalylamino;
N-arylcarbamoyl;

guanidinocarbonylamino;

arenesulfonamido or alkanesulfonamido,
which may have at least one suitable substituent selected from hydroxy, carboxy and halogen;

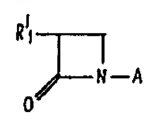
N′-aroylureido;

substituted aminooxy selected from:—

aryloxyalkanoylaminooxy;
alkylideneaminooxy;
heterocyclic-alkylideneaminooxy; and
aralkylideneaminooxy
which may have at least one suitable substituent selected from carboxy or its derivative, alkoxy,

in which the aryl and heterocyclic ring may be additionally substituted by at least one suitable substituent selected from carboxy or its derivative, amino or protected amino, hydroxy or protected hydroxy, halogen, nitro, oxo, carbazoyl, alkanoyl, alkyl, alkoxy, aryl, aralkyl, alkanoylamino; and in all of the above groups, any aliphatic moiety or radical may comprise 1—8 carbon atoms, preferably 1—4 carbon atoms and may be additionally substituted by at least one suitable substituent selected from carboxy or its derivative, amino or protected amino, azido, nitro, halogen, hydroxy, sulfo; further, in the above definition, a heterocyclic radical is intended to mean mono-aliphatic or aromatic heterocyclic radical, which may be a 5—7 membered heterocycle containing at least one hetero atom selected from oxygen, nitrogen and sulfur, and a poly-aliphatic or aromatic heterocyclic radical, for example, a benzene-fused heterocyclic radical, a heterocycle-fused aryl radical, a heterocycle-fused heterocyclic radical and the like, in which the heterocyclic moiety may be a 5—7 membered heterocycle containing at least one heteroatom selected from oxygen, nitrogen and sulfur.

37. A process for preparing a compound of the formula:

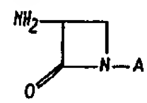


wherein
R_1' is acylamino, and
A is hydrogen,
a saturated or unsaturated normal aliphatic hydrocarbon residue, which is substituted by at least one substituent of carboxy or its derivatives, cyano, hydroxy and amino,
a saturated branched aliphatic hydrocarbon residue which is substituted by at least one substituent of carboxy or its derivatives, cyano, hydroxy and amino,

an unsaturated branched aliphatic hydrocarbon residue which is substituted by at least one substituent of carboxy or its derivatives, cyano, hydroxy and amino, or

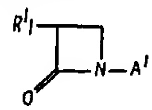
an aliphatic hydrocarbon residue substituted by carboxy or its derivatives at the first position thereof and by phenyl at the first position thereof, which may be substituted by one or more substituents selected from hydroxy, amino, nitro, alkyl, alkoxy, aralkoxy, alkylthio, halogen and sulfo;

which comprises reacting a compound of the formula:

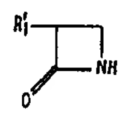


wherein A is as defined above, with an acylating agent.

38. A process for preparing a compound of the formula:



wherein R_1' is as defined in claim 37 and A′ is as defined in " A " of the claim 37 excepting hydrogen, which comprises reacting a compound of the formula:

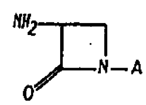


wherein R_1' is as defined in claim 37, with a N-substituting agent of the formula:

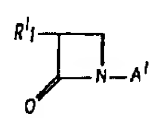
A′—X

wherein A′ is as defined above and X is an acid residue.

39. A process for preparing a compound of the formula:



wherein A is as defined in claim 37, which comprises subjecting a compound of the formula:



wherein R_1' is as defined in claim 37 and A is as defined in claim 37, to elimination reaction of the acyl group as herein defined.

40. Azetidinone derivatives of formula (I) as defined in claim 1 and salts thereof substantially as hereinbefore described in any one of the Examples.

41. The processes for preparing azetidinone derivatives of formula (I) as defined in claim 1 and salts thereof substantially as hereinbemore described in any one of the Examples.

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